Remarks

Before this Amendment, claims 1-19 were pending. By this Amendment, claims 7-15, 18, and 19 have been canceled solely in response to the Restriction Requirement. Applicants reserve the right to pursue these claims in divisional applications. Following entry of this Amendment, claims 1-6, 16, and 17 will be pending.

The rejections under 35 U.S.C. §112

Written description

Claims 1-6, 16, and 17 were rejected for lack of written description.

In order to provide an adequate written description, the specification must reasonably convey to the artisan that the inventor had possession of the claimed subject matter. *Fiers v. Revel*, 984 F.2d 1164, 1170, 25 U.S.P.Q.2d 1601, 1606 (Fed. Cir. 1993). While a patent applicant does not have to describe exactly the subject matter claimed, the description must clearly allow persons of ordinary skill in the art to recognize that the applicant invented what is claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991) (citing *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989).

In one aspect of this rejection, the Office Action, at page 5, stated that overlays are the most useful method to compare PXRD data and an x-ray diffraction pattern is like a fingerprint. The Office Action then stated: "Applicant has not

provided why the certain peaks found in the claims are the only required peaks in the x-ray diffraction pattern or the signals in the ^{13}C NMR that must match."

As understood, the Office Action is requiring the Applicants to have explained why they chose to define their invention in terms of the PXRD peaks and ^{13}C NMR signals that are recited in the claims.

The Applicants know of no requirement that applicants describe why they defined their invention in the manner claimed. The general rule is that applicants are allowed to define their invention as they see fit. *See In re Chandler*, 319 F. 2d 211, 225, 138 U.S.P.Q. 138, 148 (CCPA 1963): "The right of applicants to freedom of choice in selecting phraseology which truly points out and defines their inventions should not be abridged."

Failing to provide reasons why the claims are defined in a particular manner does not give rise to a lack of written description. The only possible relevant inquiry with respect to written description raised by the Office Action's comments is whether the recitation of the PXRD peaks and ^{13}C NMR signals in the claims would lead one of ordinary skill in the art to doubt that the Applicants possessed or had invented the crystalline form that is being claimed.

This is clearly not the case. The specification clearly conveys to one of ordinary skill in the art that the Applicants possessed and had invented a crystalline form of atorvastatin referred to as "Form V" that is defined by the PXRD peaks and ^{13}C NMR signals recited in the claims.

It is well established in the art of the analysis of polymorphs of pharmaceutical compounds that a PXRD pattern or ^{13}C NMR spectrum is characteristic of a particular

polymorph and is used in the art to distinguish that polymorph from other polymorphs. The scientific and patent literature demonstrate that PXRDs and solid state ^{13}C NMR are acceptable ways of characterizing polymorphs, including polymorphs of atorvastatin. See, e.g., Wall, Pharmaceutical Manufacturing, February, 1986, Vol. 3, No. 2, pp.33-42 (Exhibit A), at p. 35, right column:

> The most definitive analysis of crystalline-state structure is given by x-ray diffraction studies. Diffraction patterns may be obtained from either a single crystal or a powdered specimen. In single-crystal studies, the x-ray reflection angles off of the rotating crystal are compiled, and interatomic distances, ring planes, and dihedral angles are determined based on these angles. More commonly in polymorphic studies, however, x-ray diffractograms of powdered samples are compared for qualitative differences. [emphasis added]

See also Rouhi, "The Right Stuff," Chemical & Engineering News, February 24, 2003, pp. 32-35 (cited in the current Office Action), at p. 32:

> Polymorphs arise when molecules of a compound stack in the solid state in distinct ways. Although identical in chemical composition, polymorphs can have very different properties. They are distinguishable by various analytical techniques, especially X-ray powder diffraction. [emphasis added]

Form V is described in the present application as being characterized by, inter alia: (1) a PXRD pattern having peaks at 5.3 ±0.2 and 8.3 ±0.2 degrees 2θ and a broad peak at 18-23 +/- 0.2 degrees 2θ with a maximum at 18.3 +/- 0.2 degrees 2θ; and (2) solid state ^{13}C NMR signals at 21.9, 25.9, 118.9, 122.5, 128.7, 161.0 and 167.1 ppm. See, for example, page 5 of the present specification, lines 13-15 (PXRD peaks) and original claim 5 (^{13}C NMR signals).

From the descriptions of PXRD peaks and ^{13}C NMR signals in the present application referred to in the preceding paragraph, one of ordinary skill in the art

would understand that the inventors of the present application possessed and had invented a polymorph of atorvastatin calcium referred to in the present application as Form V at least as early as the filing date of the present application.

The Office Action provided no evidence that one of ordinary skill in the art would doubt that the Applicants possessed or had invented the claimed invention in view of the disclosures of the present invention. Assuming the Office Action is correct and that an x-ray diffraction pattern is like a fingerprint, this would support the Applicant's position. The recited PXRD peaks, like distinguishing whorls and other characteristics of fingerprints, convey to one of ordinary skill in the art that the Applicants possessed and invented Form V.

In another aspect of this rejection, the Office Action, at pages 5-7, finds a lack of written description because the claims do not recite all the PXRD peaks or ^{13}C NMR signals of Form V and because the specification does not explain why all the PXRD peaks or ^{13}C NMR signals are not recited. See the sentence bridging pages 5 and 6:

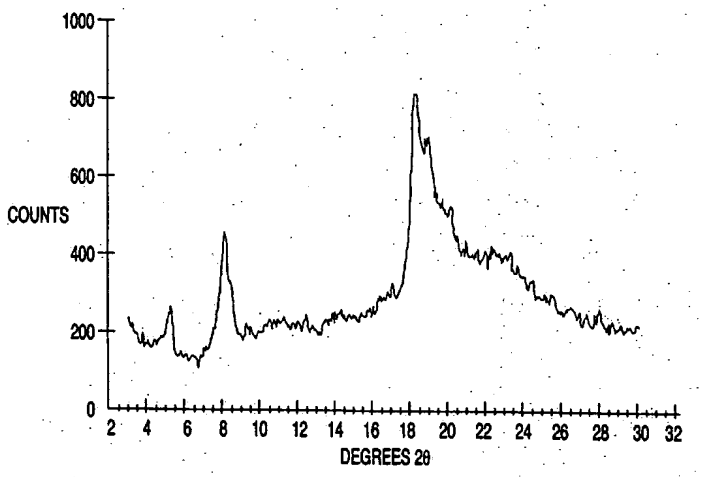
> The peaks present in the claims 3 and 17 and the ^{13}C NMR signals in claims 5 and 17 do not include all peaks of the x-ray diffraction pattern or all the signals in the ^{13}C NMR, nor does the specification provide any direction or guidance as to why certain peaks and signals are the only required peaks and signals in the x-ray data or the ^{13}C NMR.

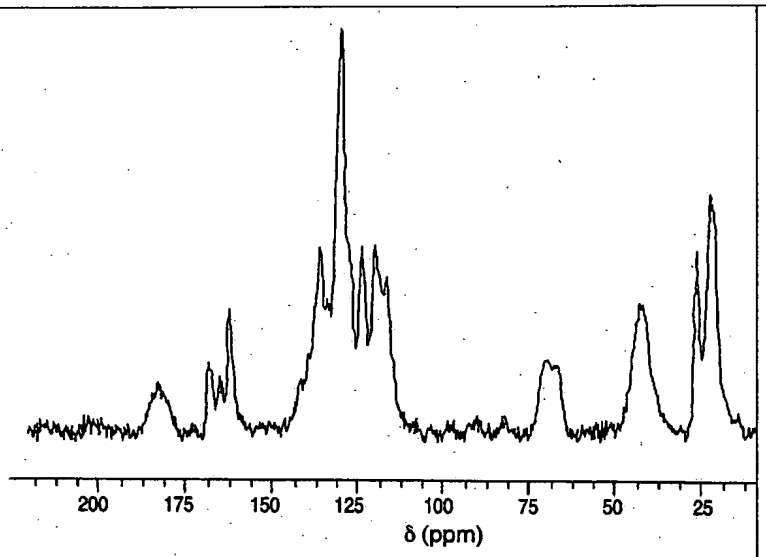
There is no requirement that a claim must recite every feature of an invention to satisfy the written description requirement. All that is required is that the specification clearly convey to one of ordinary skill in the art that the Applicants possessed or had invented what is recited in the claims. There is no need for the

claims to recite every possible of feature of the invention for the specification to accomplish this.

The chart below shows the present claims and the portions of the specification where each claim limitation is found. As can be seen, there is no doubt that, since each claim limitation is found in the specification, one of ordinary skill in the art would recognize that the Applicants possessed or had invented what is recited in the claims.

Claim limitation	**Where found in the specification**
Claim 1: Atorvastatin calcium Form V of claim 3 produced by a process comprising the steps of	
a) dissolving a metal, ammonium or alkylammonium salt of atorvastatin in a solvent to form an atorvastatin salt solution,	Page 7, lines 5-7: "The present invention further provides a process for the preparation of atorvastatin calcium Form V. The process comprises the steps of dissolving a salt of atorvastatin in a solvent to form an atorvastatin salt solution ..." Page 7, lines 10-12: "The atorvastatin salt of the present invention includes alkali metal salts, e.g. lithium, sodium, and potassium salts; alkaline-earth metal salts such as magnesium salts; as well as ammonium and alkyl, aryl or alkaryl ammonium salts."
b) contacting the atorvastatin salt solution with a calcium salt, and	Page 7, line 8: "contacting the atorvastatin salt solution with a calcium salt ..."
c) isolating crystalline atorvastatin calcium Form V.	Page 7, line 9: "isolating atorvastatin calcium in new Form V."

Claim 2: Atorvastatin calcium Form V having an X-ray powder diffractogram substantially as follows  	Figure 1
Claim 3: Atorvastatin calcium Form V characterized by X-ray powder diffraction peaks at 5.3 ±0.2 and 8.3 ±0.2 degrees 2θ and a broad peak at 18-23 +/- 0.2 degrees 2θ with a maximum at 18.3 +/- 0.2 degrees 2θ.	Page 5, lines 13-15: The X-ray powder diffractogram of Form V (Fig. 1) has two medium peaks at 5.3 ±0.2 and 8.3 ±0.2 degrees 2θ and one large peak in the range 18-23 degrees 2θ with a maximum at about 18.3 ±0.2 degrees two theta.
Claim 4: Atorvastatin calcium Form V having a solid state ^{13}C NMR spectrum substantially as follows	Figure 2

	
Claim 5: Atorvastatin calcium Form V characterized by solid state ^{13}C NMR signals at 21.9, 25.9, 118.9, 122.5, 128.7, 161.0 and 167.1 ppm.	Page 17 (original claim 5)[1]: The atorvastatin calcium Form V of claim 1 having solid state ^{13}C NMR signals at about 21.9, 25.9, 118.9, 122.5, 128.7, 161.0 and 167.1 ppm.
Claim 6: Atorvastatin calcium Form V of claim 3 containing up to about 9 moles of water per mole of atorvastatin calcium.	Page 7, lines 2-4: Thus, atorvastatin calcium Form V can be in various states of hydration, between 0 and 9 moles of water. Page 17 (original claim 6): Atorvastatin calcium Form V containing up to about 9 moles of water per mole of atorvastatin calcium.
Claim 16: A pharmaceutical composition that is a solid or suspension comprising a therapeutic amount of atorvastatin calcium Form V of claim 1, 3, or 5.	Page 18 (original claim 16): A pharmaceutical composition comprising a therapeutic amount of atorvastatin Form V or hydrates thereof of claim 1. Page 11, lines 1-2: The compositions of the invention include powders, granulates, aggregates and other solid compositions ...

[1] "It is elementary that claims contained in an application as filed may be considered part of the disclosure of the application." *In re Myers*, 410 F.2d 420, 161 USPQ 668, 673 (CCPA 1969).

	Page 12, lines 7-8: Dosage forms include solid dosage forms, like tablet, powders, capsules, suppositories, sachets, troches and losenges as well as liquid suspensions and elixirs.
Claim 17: Atorvastatin calcium Form V characterized by x-ray powder diffraction peaks at 5.3 ±0.2 and 8.3 +/- 0.2 degrees 2θ and ^{13}C NMR signals at 21.9, 25.9, 118.9, 122.5, 128.7, 161.0 and 167.1 ppm.	Page 5, lines 13-14: The X-ray powder diffractogram of Form V (Fig. 1) has two medium peaks at 5.3 ±0.2 and 8.3 ±0.2 degrees 2θ ... Page 17 (original claim 5): The atorvastatin calcium Form V of claim 1 having solid state ^{13}C NMR signals at about 21.9, 25.9, 118.9, 122.5, 128.7, 161.0 and 167.1 ppm.

At page 7, the Office Action stated:

> [T]he specification should have disclosed: (1) how the peaks or signals were selected; (2) if the peaks or signals are subject to preferred orientation effects; (3) if all of the peaks specific [sic] in the presence of excipients (see instant claim 16); and (4) if there are any perturbations after formulation.

The Applicants note that, having conveyed the concept that the Applicants possessed or had invented Form V (as shown above), the specification need have done nothing more to satisfy the written description requirement. There was no need to disclose any of the items (1)-(4) mentioned above.

The Office Action, at page 8, stated that "There is no written description in the originally field disclosure for hydrates of Atorvastatin calcium Form V ..."

While not necessarily agreeing with the above, the Applicants, in the interest of expediting prosecution, have amended the claims so that the claims no longer recite "hydrate" or "hydrates."

In view of the above, it is respectfully requested that this rejection be withdrawn.

Enablement

Claims 1-6, 16, and 17 were rejected for lack of enablement.

In one aspect, this rejection was based on the recitation of "hydrate" or "hydrates" in the claims. The claims have now been amended to no longer recite "hydrate" or "hydrates." Thus, this aspect of this rejection is moot.

At page 10 of the Office Action, it was stated that claims 3 and 5 lack enablement because they are directed to multiple crystalline forms:

> Claims 3 and 5 are claiming multiple crystalline forms of Atorvastatin calcium products as can be seen by claims 3 and 5 which state that the products are characterized by (open language) X-ray powder diffraction peaks and ^{13}C NMR signals that do not have to be those disclosed in instant Figures 1 and 2. Therefore, the claims are directed to multiple crystalline forms.

The Applicants respectfully traverse this aspect of this rejection. Reading claims 3 and 5 as being directed to multiple crystalline forms is inconsistent with both the plain language of these claims and the teachings of the specification. Claims 3 and 5 both recite "Atorvastatin calcium Form V." Thus, the plain language of these claims indicates that they are directed to a specific crystalline form of atorvastatin, Form V. This is reinforced by the specification, which teaches that the invention disclosed therein is Form V, a specific crystalline form of atorvastatin. See, e.g., page 4, line 19: "The present invention provides new Form V of atorvastatin calcium ..."; page 5, line 9: "The new crystalline form of atorvastatin calcium Form V ..."

Furthermore, the PXRD peaks and ^{13}C NMR signals recited in claims 3 and 5 are adequate to define Form V as a single crystalline form and to distinguish Form V from other crystalline forms of atorvastatin. See the specification, page 5, lines 13-18:

> **The X-ray powder diffractogram of Form V (Fig.1) has two medium peaks at 5.3±0.2 and 8.3±0.2 degrees 2θ and one large peak in the range 18-23 degrees 2θ with a maximum at about 18.3±0.2 degrees two-theta. This X-Ray pattern is well distinguished from that of known Forms I, II, III and IV and also is well distinguished from the X-Ray pattern of amorphous atorvastatin calcium which is characterized by two broad humps in the ranges 8-14 degrees 2θ and 15-26 degrees 2θ.**

See also the specification, page 6, lines 19-23:

This solid-state ^{13}C NMR spectrum (Fig. 2) is well distinguished from those of known Forms I, II, III and IV, and also is distinguished from that of the amorphous form which displays a different pattern with shifts significantly different from that of Form V at 21.0 ppm, 26.4 ppm, one broad peak in the range 60-75 ppm with a maximum at 69.7 ppm and 138.8 ppm.

F NMR spectrometer

In another aspect, this rejection was based on the argument that a pharmaceutical composition comprising Form V will convert to the free form or the thermodynamically most stable crystalline form of atorvastatin. See the Office Action, sentence bridging pages 15 and 16:

> [T]he specification fails to provide the steps of ensuring that the pharmaceutical compositions will maintain the specific forms as found in the specification and will not resort back to the free form or the most thermodynamically stable form of the compound.

The Applicants presume this aspect of this rejection is directed to claim 16, which is the only pending claim directed to a pharmaceutical composition.

With respect to possible conversion to the free form, the Office Action stated, at the paragraph bridging pages 13 and 14:

> The state of the prior art is that an acceptable carrier for a pharmaceutical formulation can be water, which embraces a suspension. Dissolving a specific crystalline form in water, creating an aqueous solution, would put the compound in its free form and not in a crystalline form ...

The Applicants wish to point out that conversion to the free form is inconsistent with the plain language of claim 16. Claim 16 recites that the claimed pharmaceutical composition "is a solid or suspension ... of atorvastatin calcium Form

V." Thus, to be within the scope of claim 16 requires the presence of the Form V crystalline form, either as a solid or in suspension. A pharmaceutical composition in which all of the atorvastatin is in free form is outside the scope of claim 16. There is no requirement that the specification enable subject matter that is outside the scope of the claims.

With respect to possible conversion to the most stable form, the Applicants submit that the evidence cited in the Office Action is inadequate to support this aspect of the rejection.

The specification teaches that the claimed atorvastatin Form V can be formulated into pharmaceutical compositions (see pages 11-13). Thus, the specification teaches that Form V will persist after being formulated into pharmaceutical compositions. The burden is on the U.S. Patent and Trademark Office to provide evidence or reasoning as to why this teaching of the specification is incorrect. See *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1971), where the United States Court of Customs and Patent Appeals stated:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein .... [italics in original]
>
> 439 F.2d at 223, 169 U.S.P.Q. at 369.
>
> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. [italics in original; underscoring added]

439 F.2d at 224, 169 U.S.P.Q. at 370.

The Office Action has not met this burden. A premise of this rejection is that the act of formulating Form V into a pharmaceutical composition will result in the conversion of Form V into other forms. See the Office Action, page 13:

> The state of the prior art is that the preparation of pharmaceutical compositions requires creating solutions, milling, adding diluents, excipients, surfactants, etc. The process of preparing a pharmaceutical composition will cause a specific crystalline form, if in the metastable state, to resort back to the most thermodynamically stable form, which is the form with the lowest vapor pressure. Polymorphs tend to convert from less stable to more stable forms (Rouhi, page 32).

This aspect of the rejection goes far beyond the evidence that the Office Action cited. It should be noted that claim 16 contains no limitations requiring all of the atorvastatin in the composition to be Form V or requiring Form V to persist for any particular length of time in the composition. The Office Action cited no evidence to support the premise that all of the Form V is likely to convert so rapidly and so completely into the most stable form when formulated into a pharmaceutical composition that a person skilled in the art could not practice the invention defined in claim 16.

The cited evidence that mentions the conversion of crystalline forms[2] is Rouhi, Chemical and Engineering News, February 24, 2003, pages 32-35 (Rouhi); Concise Encyclopedia of Chemistry, 1993, Walter de Gruyter, Berlin-New York, pages 872-873; Haleblian et al., 1969, J. Pharm. Sci. 58:911-929 (Haleblian), and U.S.

[2] While other publications are cited in the Office Action, they do not address the issue of conversion of one crystalline form into another.

Pharmacopia #23, National Formulary #18 (1995), pages 1843-1844, entry (941), X-Ray Diffraction (U.S. Pharmacopia).

Rouhi at most shows that metastable forms tend to, i.e., may possibly, convert to the most thermodynamically stable form. See the Office Action, page 13: "Polymorphs tend to convert from less stable to more stable forms (Rouhi, page 32)." Rouhi says nothing about the likelihood, the speed of, or the completeness of, such a conversion. In particular, Rouhi says nothing about the conversion of crystalline forms of atorvastatin.

Rather than supporting this aspect of the rejection, the Concise Encyclopedia of Chemistry supports the Applicants' position by providing evidence that Form V will likely be stable long enough to be formulated into pharmaceutical compositions. See page 873, left column: "Often, the conversion rate in the solid phases is so slow that even modifications which are unstable under the conditions can be kept for a long time ..."

Haleblian also provides evidence in support of the Applicants' position. See page 913: "For example, phase conversion may be so slow in certain ointment bases that a more soluble metastable form may be safely used. It is entirely possible the use of a more thermodynamically energetic form of the drug may results in a more efficacious therapeutic formulation." See also page 927, left column: "Many minerals (argonite, anatase, brookite, etc.), many drugs (75) (atophane, progesterone, estrone, marfanil, sulfathiazole, veronal, etc.), and even some important metals (copper, silver, zinc, tin, bismuth, and cadmium) are used daily in the metastable form."

The U.S. Pharmacopia also provides evidence to support the Applicants' position by stating that conversion can be "quite slow." See page 1843:

> Many compounds are capable of crystallizing in more than one type of crystal lattice. At any particular temperature and pressure, only one crystalline form (polymorph) is thermodynamically stable. Since the rate of phase transformation of a metastable polymorph to the stable one can be quite slow, it is not uncommon to find several polymorphs of crystalline pharmaceutical compounds existing under normal handling conditions.

The only basis given in the Office Action for this aspect of the rejection is the speculation that if Form V is subjected to the usual procedures for making pharmaceutical compositions it will convert to other forms. The Office Action provided no evidence in support of this speculation. In fact, the evidence cited by the Office Action leads to a conclusion opposite to that of the Office Action, i.e., that Form V will likely be stable long enough to be formulated into pharmaceutical compositions.

Furthermore, Rouhi teaches that the Office Action's speculation is wrong. Rouhi teaches that the likely outcome of formulating a crystalline form, when carried out by those skilled in the art, is that the crystalline form would maintain itself for a reasonable period of time such that the pharmaceutical composition would be useful. This is part of the teachings of Rouhi since one of the main themes in Rouhi is that pharmaceutical companies are actively seeking new crystalline forms of compounds (even metastable forms) in order to formulate these new crystalline forms into pharmaceutical compositions (see page 32, right column; "[M]uch effort is being expended looking for metastable forms of currently marketed drugs whose stable forms have been around for a long time." It would make no sense for pharmaceutical

companies to behave in such a manner if the speculation underlying this rejection were correct.

In addition, other evidence demonstrates that less stable crystalline forms can co-exist with the most stable crystalline form for a long time. See Exhibit B (Byrn, S.R., et al., "Drugs as Molecular Solids," Solid State Chemistry of Drugs, 2nd edition, 1999, SSCI Inc., West Lafayette, IN, Chapter 1), at page 16:

> Use of the term "equilibrium" in connection with crystallizing systems requires clarification. When a substance exists in more than one crystal form, that is, when other polymorphs are possible, only *the least soluble* of these at a *given* temperature is considered the most physically stable form at that temperature, all others are considered to be **metastable forms**. In given cases, a solution of a substance may be in apparent equilibrium with one of the metastable phases for a long time, in which case, the system is in metastable equilibrium and is expressing the thermodynamic solubility of *that* solid form. [italics and bold in original; underscoring added]

The quotations above show that, in making this aspect of the rejection, the Office Action ignored the fact that, even if conversion to a more stable form occurs, conversion may be "quite slow" or may take a "long time." In this context, the Applicants note that the Office Action states, at page 12: "Often the conversion rate in the solid phases is so slow that even modifications, which are unstable under the conditions, can be kept for a long time in their metastable state."

Thus, the evidence of record indicates that the likely outcome of formulating Form V into pharmaceutical compositions is that Form V will persist, at least for a period of time sufficient to provide a useful pharmaceutical composition.

In view of the above, it can be seen that the evidence provided in the Office Action is inadequate to support this aspect of the rejection. Thus, the Office Action

failed to provide "acceptable evidence or reasoning" to support this aspect of the rejection, as required by *Marzocchi*.

In view of the above, it is respectfully requested that this rejection be withdrawn.

Indefiniteness

Claims 1-6, 16, and 17 were rejected as being indefinite.

In one aspect, this rejection was based on the recitation of "hydrate" or "hydrates" in the claims. The claims have now been amended to no longer recite "hydrate" or "hydrates." Thus, this aspect of this rejection has been rendered moot.

In another aspect, this rejection was based on the recitation of "substantially" in claims 2 and 4. Claims 2 and 4 have now been amended to no longer recite "substantially." Thus, this aspect of this rejection has been rendered moot.

In view of the above, it is respectfully requested that this rejection be withdrawn.

The rejections under 35 U.S.C. §102(b)

Claims 1-6, 16, and 17 were rejected as being anticipated by U.S. Patent No. 5,686,104 (Mills); International Patent Publication WO 97/03959 (Briggs); or U.S. Patent No. 5,273,995 (Roth).

The entire argument in support of these rejections consists of the following two sentences on page 22 of the Office Action:

> Each of the above cited prior art disclose products which are embraced by the instant claimed invention. Therefore, each of the above cited prior art anticipates the instant claimed invention.

These two sentences are completely conclusory; there is no reasoned argument in them to support these anticipation rejections. For example, there is no discussion of where the claim elements are found in the cited documents. The burden of establishing a *prima facie* case of anticipation resides with the U.S. Patent and Trademark Office (see *In re Skinner*, 2 U.S.P.Q. 2d 1788, 1788-1789 (Bd. Pat. App. & Int. 1987)). In view of the lack of reasoned argument supporting this rejection, a *prima facie* case of anticipation has not been made out.

For the sake of completeness, the Applicants explain below why none of Briggs, Mills, or Roth discloses the claimed crystalline Form V atorvastatin.

Briggs

Briggs discloses 3 crystalline forms, referred to as Form I, Form II, and Form IV.

Form I

Briggs discloses that Form I has PXRD peaks and ^{13}C NMR signals different from the PXRD peaks and ^{13}C NMR signals of Form V recited in the present claims.

Claim 3 requires a PXRD peak at 5.3 ± 0.2 degrees 2θ (i.e., between 5.1 - 5.5 degrees 2θ), a PXRD peak at 8.3 ± 0.2 degrees 2θ (i.e., between 8.1 - 8.5 degrees 2θ), and a broad peak at 18-23 +/- 0.2 degrees 2θ with a maximum at 18.3 +/- 0.2 degrees 2θ (i.e., a broad peak between 17.8-23.2 degrees 2θ with a maximum at 18.1-18.5 degrees 2θ).

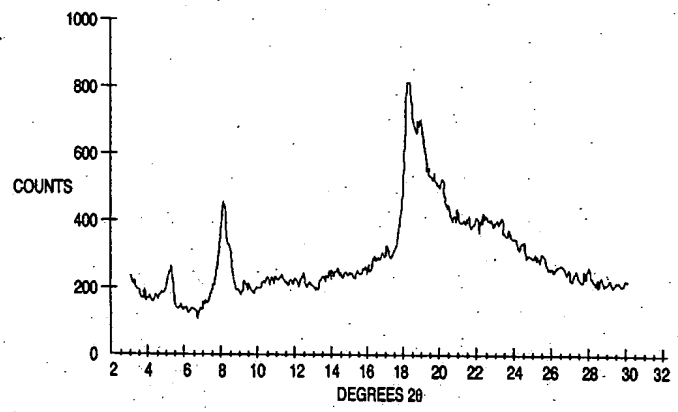
Form I of Briggs does not meet these limitations of claim 3 because Form I does not have a peak between 5.1 - 5.5 degrees 2θ or between 8.1 - 8.5 degrees 2θ. Form I also does not have a broad peak between 17.8-23.2 degrees 2θ with a maximum at 18.1-18.5 degrees 2θ. See the table on page 4 of Briggs (reproduced below), which shows the PXRD peaks of Form I.

2θ	d	Relative Intensity (>20%) Ground 2 Minutes
9.150	9.6565	42.60
9.470	9.3311	41.94
10.266	8.6098	55.67
10.560	8.3705	29.33
11.853	7.4601	41.74
12.195	7.2518	24.62
17.075	5.1887	60.12
19.485	4.5520	73.59
21.626	4.1059	100.00
21.960	4.0442	49.44
22.748	3.9059	45.85
23.335	3.8088	44.72
23.734	3.7457	63.04
24.438	3.6394	21.10
28.915	3.0853	23.42
29.234	3.0524	23.36

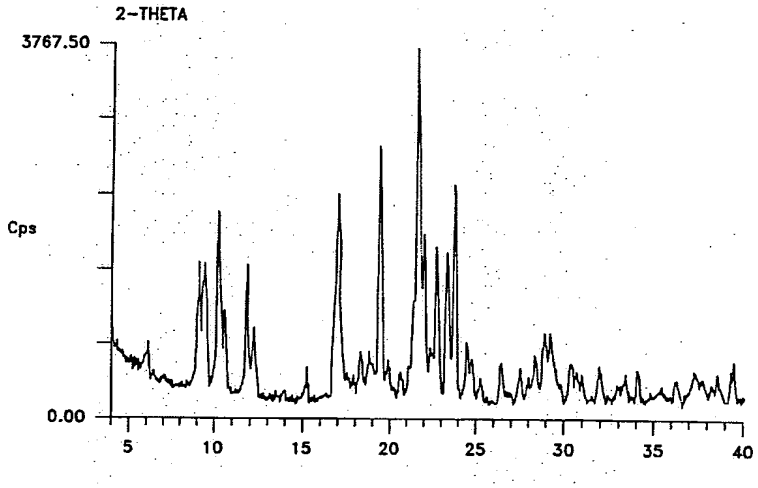
Thus, Form I of Briggs does not anticipate claim 3.

Claim 1 depends from claim 3. Thus, Form I of Briggs does not anticipate claim 1.

Claim 2 is directed to atorvastatin calcium Form V having a PXRD pattern as shown in claim 2. This PXRD pattern is not the same as the PXRD pattern of Form I of Briggs, as the comparison of the pattern shown in claim 2 with Figure 1 of Briggs below demonstrates. Figure 1 of Briggs is the PXRD pattern of Form I.

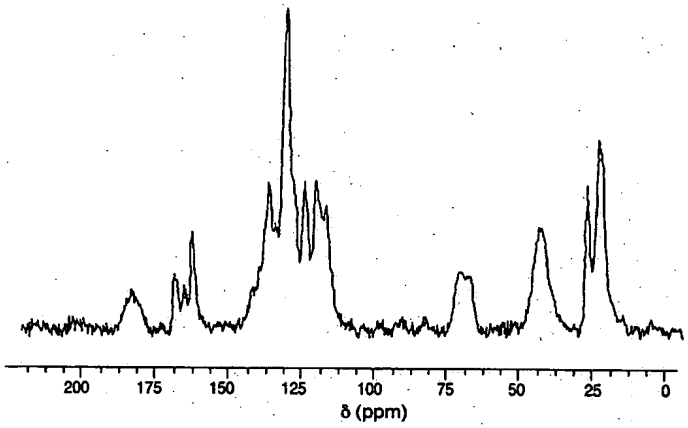


FIG–1

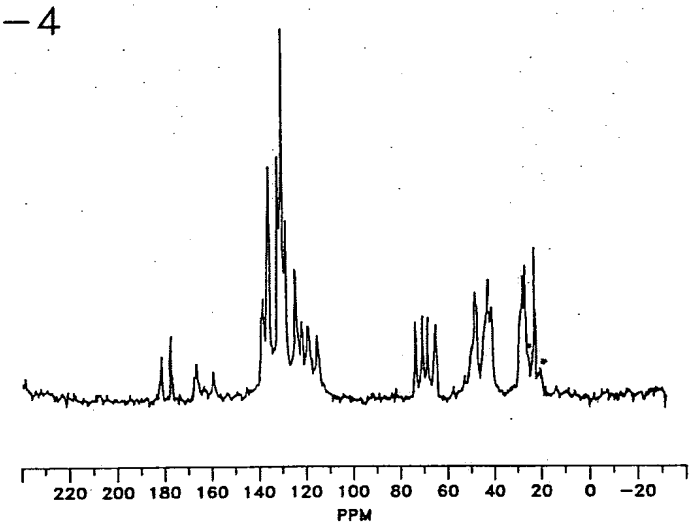


Among the differences between Form V and Form I is the prominent set of peaks centered around 10 degrees 2θ in Form I that are not present in the Form V spectrum. Another clear difference is a strong peak at about 17 degrees 2θ in Form I that is lacking in the Form V spectrum. Given these differences, it cannot be argued that the PXRD pattern of Form I is the same as the PXRD pattern depicted in claim 2. Therefore, Form I of Briggs does not anticipate claim 2.

Claim 4 is directed to atorvastatin calcium Form V having a ^{13}C NMR spectrum as shown in claim 4. This ^{13}C NMR spectrum is not the same as the ^{13}C NMR spectrum of Form I of Briggs, as the comparison of the ^{13}C NMR spectrum shown in claim 2 with Figure 4 of Briggs below demonstrates. Figure 4 of Briggs is the ^{13}C NMR spectrum of Form I.



FIG—4



Among the differences between Form V and Form I is the difference in the group of peaks between about 20 ppm and 80 ppm. The pattern of these peaks is

quite different between these two forms. Given this difference, it cannot be argued that the ^{13}C NMR spectrum of Form I is the same as the ^{13}C NMR spectrum depicted in claim 4. Therefore, Form I of Briggs does not anticipate claim 4.

Claim 5 requires a ^{13}C NMR spectrum characterized by signals at 21.9, 25.9, 118.9, 122.5, 128.7, 161.0 and 167.1 ppm.

Form I of Briggs does not meet these limitations of claim 5 because Form I does not have any of these signals. See the table on page 5 of Briggs (reproduced below), which shows the ^{13}C NMR signals of Form I.

Assignment (7 kHz)	Chemical Shift
C12 or C25	182.8
C12 or C25	178.4
C16	166.7 (broad) and 159.3
Aromatic Carbons	
C2-C5, C13-C18, C19-C24, C27-C32	137.0
	134.9
	131.1
	129.5
	127.6
	123.5
	120.9
	118.2
	113.8
C8,C10	73.1
	70.5
	68.1
	64.9
Methylene Carbons	
C6, C7, C9, C11	47.4
	41.9
	40.2
C33	26.4
	25.2
C34	21.3

Thus, Form I of Briggs does not anticipate claim 5.

Claim 6 depends from claim 3 and, since Form I of Briggs does not anticipate claim 3, Form I of Briggs also does not anticipate claim 6.

Claim 16 depends from claim 1, claim 3, or claim 5 and, since Form I of Briggs does not anticipate claim 1, claim 3, or claim 5, Form I of Briggs also does not anticipate claim 16.

Claim 17 is directed to Form V characterized by an x-ray powder diffraction peak at 5.3 ± 0.2 degrees 2θ (i.e., between 5.1 - 5.5 degrees 2θ), a peak at 8.3 ± 0.2 degrees 2θ (i.e., between 8.1 - 8.5 degrees 2θ), and ^{13}C NMR signals at 21.9, 25.9, 118.9, 122.5, 128.7, and 167.1 ppm. As discussed above in connection with claim 3, Form I does not have a peak between 5.1 - 5.5 degrees 2θ or between 8.1 - 8.5 degrees 2θ. As discussed above in connection with claim 5, Form I does not have ^{13}C NMR signals at 21.9, 25.9, 118.9, 122.5, 128.7, 161.0, and 167.1 ppm. Accordingly, Form I of Briggs does not anticipate claim 17.

Form II

Briggs discloses that Form II has PXRD peaks and ^{13}C NMR signals different from the PXRD peaks and ^{13}C NMR signals of Form V recited in the present claims.

Claim 3 requires a PXRD peak at 5.3 ± 0.2 degrees 2θ (i.e., between 5.1 - 5.5 degrees 2θ), a PXRD peak at 8.3 ± 0.2 degrees 2θ (i.e., between 8.1 - 8.5 degrees 2θ), and a broad peak at 18-23 +/- 0.2 degrees 2θ with a maximum at 18.3 +/- 0.2 degrees 2θ (i.e., a broad peak between 17.8-23.2 degrees 2θ with a maximum at 18.1-18.5 degrees 2θ).

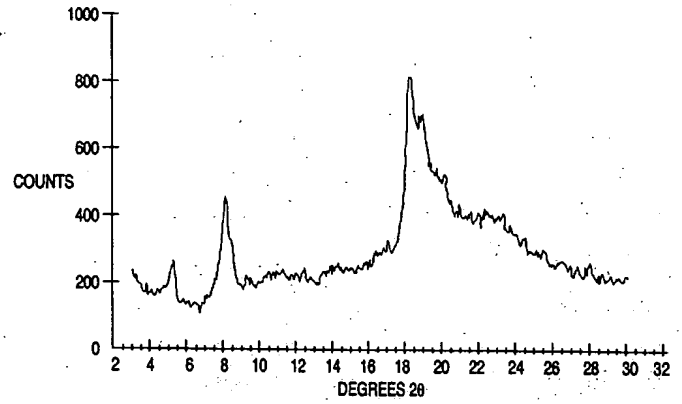
Form II of Briggs does not meet these limitations of claim 3 because Form II does not have a peak between 5.1 - 5.5 degrees 2θ or a peak between 8.1 - 8.5 degrees 2θ. Form II also does not have a broad peak between 17.8-23.2 degrees 2θ with a maximum at 18.1-18.5 degrees 2θ. See the table on page 6 of Briggs (reproduced below), which shows the PXRD peaks of Form II.

2θ	d	Relative Intensity (>20%) Ground 2 Minutes
5.582	15.8180	42.00
7.384	11.9620	38.63
8.533	10.3534	100.00
9.040	9.7741	92.06
12.440 (broad)	7.1094	30.69
15.771 (broad)	5.6146	38.78
17.120-17.360 (broad)	5.1750-5.1040	63.66-55.11
19.490	4.5507	56.64
20.502	4.3283	67.20
22.706-23.159 (broad)	3.9129-3.8375	49.20-48.00
25.697 (broad)	3.4639	38.93
29.504	3.0250	37.86

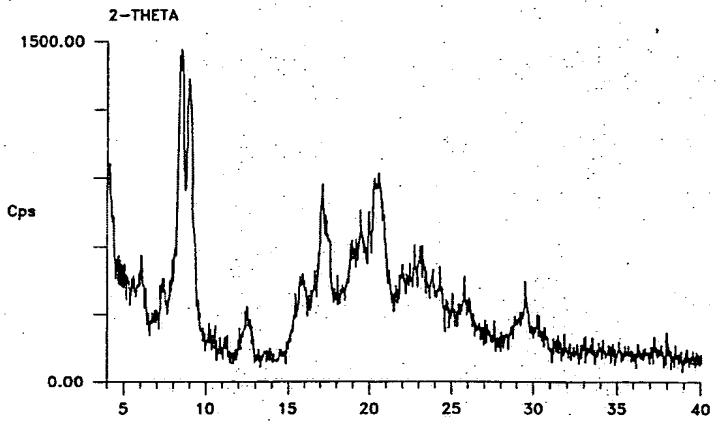
Thus, Form II of Briggs does not anticipate claim 3.

Claim 1 depends from claim 3. Thus, Form II of Briggs does not anticipate claim 1.

Claim 2 is directed to atorvastatin calcium Form V having a PXRD pattern as shown in claim 2. This PXRD pattern is not the same as the PXRD pattern of Form II of Briggs, as the comparison of the pattern shown in claim 2 with Figure 2 of Briggs below demonstrates. Figure 2 of Briggs is the PXRD pattern of Form II.

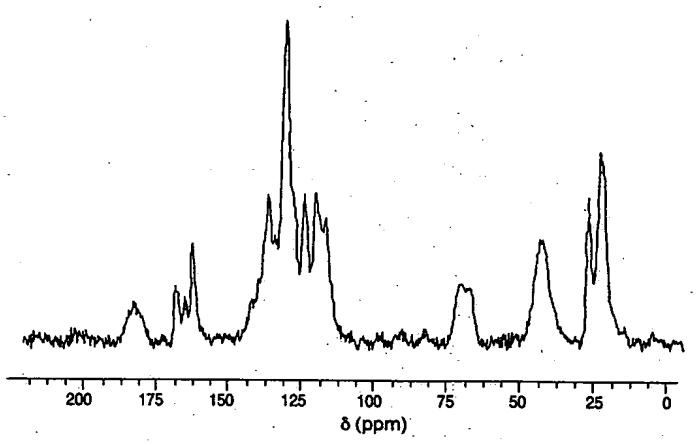


FIG–2

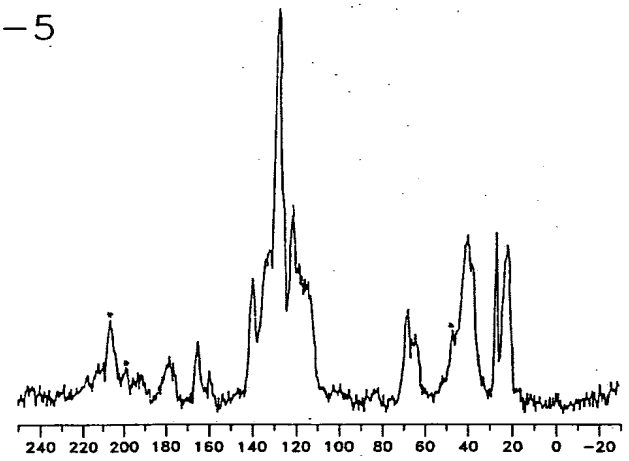


Among the differences between Form V and Form II is the prominent double peak at about 8.5 degrees 2θ in Form II that is the largest peak in the Form II PXRD spectrum. Although Form V possesses a peak in the same general area, the Form V peak is much less prominent and is not the largest peak in the Form V PXRD spectrum. Given this difference, it cannot be argued that the PXRD pattern of Form II is the same as the PXRD pattern depicted in claim 2. Therefore, Form II of Briggs does not anticipate claim 2.

Claim 4 is directed to atorvastatin calcium Form V having a ^{13}C NMR spectrum as shown in claim 4. This ^{13}C NMR spectrum is not the same as the ^{13}C NMR spectrum of Form II of Briggs, as the comparison of the ^{13}C NMR spectrum shown in claim 2 with Figure 5 of Briggs below demonstrates. Figure 5 of Briggs is the ^{13}C NMR spectrum of Form II.



FIG–5



Among the differences between Form V and Form II is the difference in the group of peaks between about 150 ppm and 220 ppm. The pattern of these peaks is quite different between these two forms. Given this difference, it cannot be argued

that the ^{13}C NMR spectrum of Form II is the same as the ^{13}C NMR spectrum depicted in claim 4. Therefore, Form II of Briggs does not anticipate claim 4.

Claim 5 requires a ^{13}C NMR spectrum characterized by signals at 21.9, 25.9, 118.9, 122.5, 128.7, 161.0 and 167.1 ppm.

Form II of Briggs does not meet these limitations of claim 5 because Form II does not have any of these signals, with the exception of the signal at 161.0 ppm. See the table on page 7 of Briggs (reproduced below), which shows the ^{13}C NMR signals of Form II .

Assignment	Chemical Shift
Spinning Side Band	209.1
Spinning Side Band	206.8
C12 or C25	181 (broad)
C12 or C25	163 (broad)
C16	161 (broad)
Aromatic Carbons	
C2-C5, C13-C18, C19-C24, C27-C32	140.5
	134.8
	133.3
	129.0
	122.9
	121.4
	120.3
	119.0
	117.1
	115.7
	114.7
C8, C10	70.6
	69.0
	68.0
	67.3
Spinning Side Band	49.4
Spinning Side Band	48.9
Methylene Carbons	
C6, C7, C9, C11	43.4
	42.3
	41.7
	40.2
C33	27.5
C34	22.8 (broad)

Thus, Form II of Briggs does not anticipate claim 5.

Claim 6 depends from claim 3 and, since Form II of Briggs does not anticipate claim 3, Form II of Briggs also does not anticipate claim 6.

Claim 16 depends from claim 1, claim 3, or claim 5 and, since Form II of Briggs does not anticipate claim 1, claim 3, or claim 5, Form II of Briggs also does not anticipate claim 16.

Claim 17 is directed to Form V characterized by an x-ray powder diffraction peak at 5.3 ± 0.2 degrees 2θ (i.e., between 5.1 - 5.5 degrees 2θ) and a peak at 8.3 ± 0.2 degrees 2θ (i.e., between 8.1 - 8.5 degrees 2θ) and ^{13}C NMR signals at 21.9, 25.9, 118.9, 122.5, 128.7, and 167.1 ppm. As discussed above in connection with claim 3, Form II does not have a PXRD peak between 5.1 - 5.5 degrees 2θ or between 8.1 - 8.5 degrees 2θ. As discussed above in connection with claim 5, Form II does not have ^{13}C NMR signals at 21.9, 25.9, 118.9, 122.5, 128.7, and 167.1 ppm. Accordingly, Form II of Briggs does not anticipate claim 17.

Form IV

Briggs discloses that Form IV has PXRD peaks and ^{13}C NMR signals different from the PXRD peaks and ^{13}C NMR signals of Form V recited in the present claims.

Claim 3 requires a PXRD peak at 5.3 ± 0.2 degrees 2θ (i.e., between 5.1 - 5.5 degrees 2θ), a PXRD peak at 8.3 ± 0.2 degrees 2θ (i.e., between 8.1 - 8.5 degrees 2θ), and a broad peak at 18-23 +/- 0.2 degrees 2θ with a maximum at 18.3 +/- 0.2 degrees 2θ (i.e., a broad peak between 17.8-23.2 degrees 2θ with a maximum at 18.1-18.5 degrees 2θ).

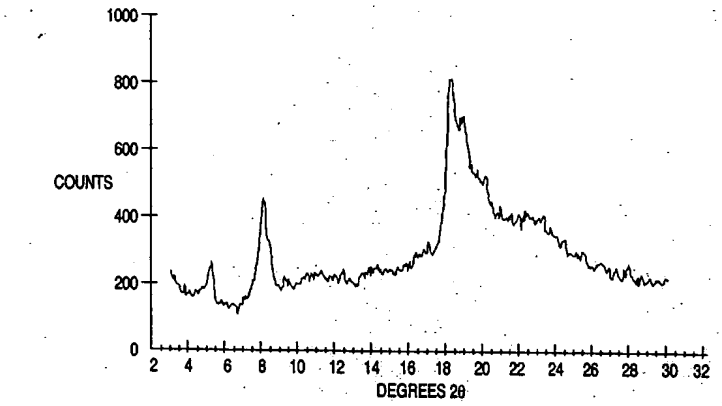
Form IV of Briggs does not meet these limitations of claim 3 because Form IV does not have a peak between 8.1 - 8.5 degrees 2θ. See the table on page 8 of Briggs (reproduced below), which shows the PXRD peaks of Form IV.

2θ	d	Relative Intensity (>15%)
4.889	18.605	38.45
5.424	16.2804	20.12
5.940	14.8660	17.29
7.997	11.0465	100.00
9.680	9.1295	67.31
10.416	8.4859	20.00
12.355	7.1584	19.15
17.662	5.0175	18.57
18.367	4.8265	23.50
19.200	4.6189	18.14
19.569	4.5327	54.79
21.723	4.0879	17.99
23.021	3.8602	28.89
23.651	3.7587	33.39
24.143	3.6832	17.23

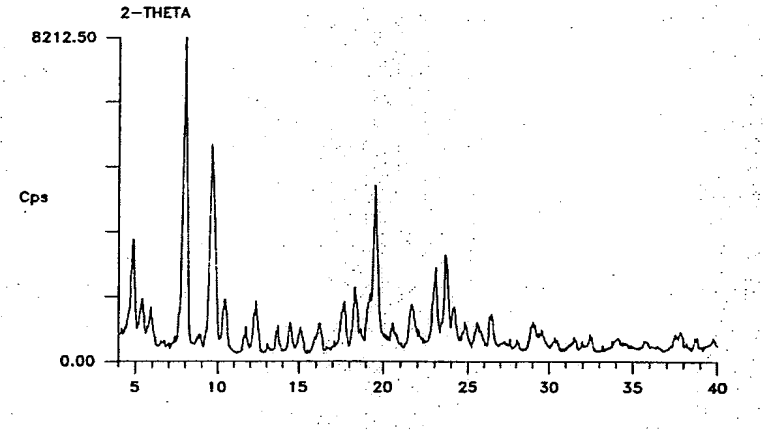
Thus, Form IV of Briggs does not anticipate claim 3.

Claim 1 depends from claim 3. Thus, Form IV of Briggs does not anticipate claim 1.

Claim 2 is directed to atorvastatin calcium Form V having a PXRD pattern as shown in claim 2. This PXRD pattern is not the same as the PXRD pattern of Form IV of Briggs, as the comparison of the pattern shown in claim 2 with Figure 3 of Briggs below demonstrates. Figure 3 of Briggs is the PXRD pattern of Form IV.



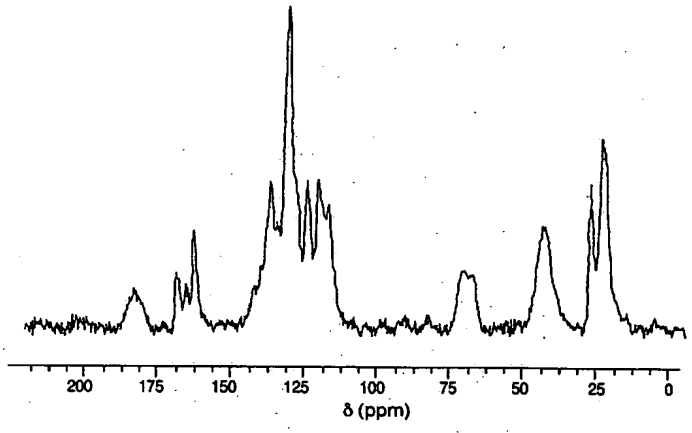
FIG–3



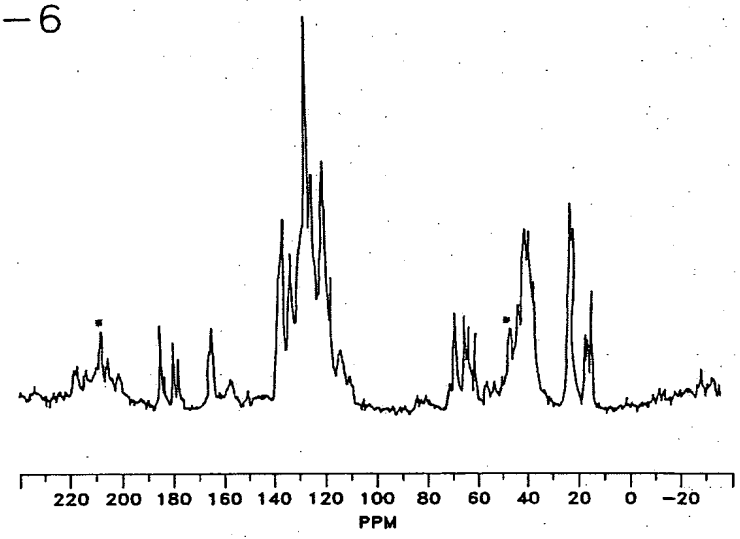
Among the differences between Form V and Form IV is the prominent peak at about 9.5 degrees 2θ in Form IV that is not present in the Form V spectrum. Given the differences in these two spectra, it cannot be argued that the PXRD pattern of Form IV is the same as the PXRD pattern depicted in claim 2. Therefore, Form IV of Briggs does not anticipate claim 2.

Claim 4 is directed to atorvastatin calcium Form V having a ^{13}C NMR spectrum as shown in claim 4. This ^{13}C NMR spectrum is not the same as the ^{13}C NMR spectrum of Form IV of Briggs, as the comparison of the ^{13}C NMR spectrum

shown in claim 2 with Figure 6 of Briggs below demonstrates. Figure 6 of Briggs is the ^{13}C NMR spectrum of Form IV.



FIG–6



Among the differences between Form V and Form IV is the difference in the patterns of the groups of peaks in the area of about 20 ppm and in the area of about 160 ppm. Given these differences, it cannot be argued that the ^{13}C NMR spectrum of Form IV is the same as the ^{13}C NMR spectrum depicted in claim 4. Therefore, Form IV of Briggs does not anticipate claim 4.

Claim 5 requires a ^{13}C NMR spectrum characterized by signals at 21.9, 25.9, 118.9, 122.5, 128.7, 161.0 and 167.1 ppm.

Form IV of Briggs does not meet these limitations of claim 5 because Form IV does not have any of these signals (except for 25.9 ppm). See the table on page 9 of Briggs (reproduced below), which shows the ^{13}C NMR signals of Form IV.

Assignment	Chemical Shift
C12 or C25	186.4
	184.9
C12 or C25	181.4
	179.3
C16	166.1 (broad)
	and
	159.0 (broad)
Aromatic Carbons	
C2-C5, C13-C18, C19-C24, C27-C32	138.1 (broad)
	134.7
	129.2
	127.1
	122.7
	119.8
	115.7
C8, C10	71.5
	67.9
	66.3
	63.5
Methylene Carbons	
C6, C7, C9, C11	46.1
	43.4
	42.1
	40.0
C33	25.9
C34	20.3
	19.4
	17.9

Thus, Form IV of Briggs does not anticipate claim 5.

Claim 6 depends from claim 3 and, since Form IV of Briggs does not anticipate claim 3, Form IV of Briggs also does not anticipate claim 6.

Claim 16 depends from claim 1, claim 3, or claim 5 and, since Form IV of Briggs does not anticipate claim 1, claim 3, or claim 5, Form IV of Briggs also does not anticipate claim 16.

Claim 17 is directed to Form V characterized by an x-ray powder diffraction peak at 8.3 ± 0.2 degrees 2θ (i.e., between 8.1 - 8.5 degrees 2θ) and ^{13}C NMR signals at 21.9, 118.9, 122.5, 128.7, and 167.1 ppm. As discussed above in connection with claim 3, Form IV does not have a peak between 8.1 - 8.5 degrees 2θ. As discussed above in connection with claim 5, Form IV does not have ^{13}C NMR signals at 21.9, 118.9, 122.5, 128.7, 161.0, and 167.1 ppm. Accordingly, Form IV of Briggs does not anticipate claim 17.

As a further difference between Briggs and the present application, it may be noted that when the processes for obtaining the crystalline forms of atorvastatin calcium of Briggs and the present application go through the sodium salt, the sodium salt is not isolated during the reaction in Briggs as it is in the present application (see Example 1). Isolating an intermediate in the process for obtaining a crystalline form can significantly effect the crystalline form thus obtained. In contrast to Briggsn the process of the present application describes obtaining a crystalline form of atorvastatin calcium, starting from an isolated sodium salt.

Mills and Roth

The Applicants respectfully traverse this rejection because both Mills and Roth disclose only amorphous atorvastatin, and not a crystalline form.

Briggs teaches that Roth discloses amorphous atorvastatin. The Applicant in Briggs is the same company that is the assignee in Roth. Briggs teaches that Roth discloses amorphous atorvastatin at page 2, lines 28-29: "The processes in the above United States Patents disclose amorphous atorvastatin ..." Among the "about United States Patents" referred to in this passage is Roth. See Briggs, page 1, line 33.

Mills is also from the same company that is the Applicant in Briggs and the assignee in Roth. Mills allegedly provides stable formulations of the atorvastatin disclosed in Roth, which is described therein as unstable. Example A of Mills is essentially the same as the procedure that is described in Example 10 of Roth. Since all other examples in Mills relate to methods for preparing formulations, the only relevant example in Mills is Example A, which results in the amorphous form, since that is form that Example 10 of Roth produces.

Even without the evidence above that Mills and Roth disclose amorphous atorvastatin rather than a crystalline form, it would be clear that Mills and Roth do not anticipate the present claims. Neither Mills nor Roth disclose crystalline forms of atorvastatin having the PXRD peaks, PXRD spectrum, ^{13}C NMR signals, or ^{13}C NMR spectrum recited in the present claims. In fact, no data with respect to PXRD or ^{13}C NMR of atorvastatin crystalline forms are provided by Mills and Roth. In view of this lack of disclosure of the PXRD or ^{13}C NMR data recited in the claims, Mills and Roth cannot support an anticipation rejection of the present claims.

The Applicants note that Mills and Roth do not shift the burden of proof with respect to anticipation onto the Applicants. That is, Mills and Roth do not require the Applicants to provide experimental evidence that the atorvastatin produced by Mills and Roth was not the presently claimed Form V.

The Applicants recognize that when claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the U.S. Patent and Trademark Office can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of the claimed products.

However, in this application, there has been no showing that the atorvastatin disclosed in Mills and Roth is identical or substantially identical to, or is produced by identical or substantially identical processes, as Form V. Rather, the evidence is strong that the atorvastatin of Mills and Roth is not the same as Form V. Thus, the burden of proof with respect to anticipation has not been shifted to the Applicants.

The only characteristic shared between Mills and Roth and the present claims is the characteristic of being a form of atorvastatin.

Against this meager evidence of identity, there is abundant evidence even beyond that in Mills, Roth, and Briggs discussed above that shows that the atorvastatin of Mills and Roth is almost surely different from the claimed Form V. This evidence shows that:

(1) many crystalline forms of atorvastatin exist;

(2) the use of different reaction conditions, and especially different solvents, in methods of preparing crystalline forms of atorvastatin leads to the production of different crystalline forms; and

(3) Mills and Roth used different solvents to prepare atorvastatin as compared to the solvents used to produce the presently claimed Form V.

The evidence of record thus shows that, rather than being the same as the claimed Form V, it is virtually certain that the forms of Mills and Roth are different from Form V.

(1) That many crystalline forms of atorvastatin exist is clear from the evidence. For example, WO 97/03959 discloses 3 crystalline forms, referred to as Form I, Form II, and Form IV. U.S. Patent No. 6,121,461 (McKenzie)[3] discloses a crystalline form referred to as Form III. U.S. Patent No. 6,605,729[4] discloses 15 crystalline forms (referred to therein as Forms V-XIX).

(2) The evidence also shows that the use of different reaction conditions, and especially different solvents, in methods of preparing crystalline forms of atorvastatin leads to the production of different crystalline forms. For example, U.S. Patent No. 6,605,729 used a mixture of acetone and water to produce Form VII; a mixture of tetrahydrofuran and water to produce Form XII; and a mixture of acetonitrile and water to produce Form XV.

(3) Mills and Roth used different methods, and in particular different solvents, from the methods and solvents used by the Applicants. Mills and Roth both prepared atorvastatin from EtOAc and hexane. The Applicants did not prepare Form V from

[3] This patent was disclosed in the Information Disclosure Statement filed July 25, 2001.

EtOAc and hexane; instead the Applicants prepared Form V from mixtures of water and ethanol, water and methanol, or tetrahydrofuran.

The evidence of record clearly shows that Mills and Roth used very different methods from those of the Applicants. Accordingly, the only reasonable conclusion to be drawn is that Mills and Roth almost certainly did not produce Form V.

In view of this conclusion, the showing necessary to shift the burden of proof to the Applicants with respect to the issue of anticipation has not been made. Accordingly, a *prima facie* case of anticipation does not exist.

A finding that a *prima facie* case of anticipation does not exist is proper in view of *Ex parte Havens*, 2003 WL 21279863 (Board of Patent Appeals & Interferences, date unavailable),[5] a case that dealt with facts similar to those here.

In *Havens*, the Board of Patent Appeals & Interferences reversed an anticipation rejection of claims directed to particular crystalline forms of a pharmaceutical compound, delavirdine mesylate, over a prior art reference that disclosed the same pharmaceutical compound, but not the particular claimed crystalline forms. The Board explained that such a fact pattern was insufficient to shift the burden of proof to the applicants:

> When the inherent properties of a prior art product are at issue, "the examiner must provide some evidence or scientific reasoning to establish the reasonableness of the examiner's belief that the functional limitation is an inherent characteristic of the prior art" before the burden is shifted to the applicant to disprove the inherency. Ex parte Skinner, 2 USPQ2d 1788, 1789 (Bd. Pat. App. Int. 1986).

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[4] This patent was disclosed in the Supplemental Information Disclosure Statement filed February 16, 2006.

[5] A copy of this decision is provided herewith as Exhibit C.

> Here, the claims on appeal are not directed to delavirdine mesylate per se, but are limited to the S and T crystal forms of that compound. Therefore, to anticipate the claims, the prior art must disclose delavirdine mesylate in the S and T crystal forms. The examiner has provided no evidence or scientific reasoning to show that the delavirdine mesylate disclosed and claimed by Palmer is in either the S or T crystal form. Therefore, the examiner has not made out a prima facie case of anticipation by inherency.
>
> The examiner's attempt to shift the burden of proof to Appellants was premature. The burden shifts to the applicant only if the examiner can show, by evidence or scientific reasoning, a reasonable basis for concluding that the prior art product meets all the limitations of the claims. The examiner has provided no basis for such a conclusion in this case. The rejection under 35 U.S.C. § 102 is reversed.
>
> *Ex parte Havens*, page 3.

A finding that a *prima facie* case of anticipation does not exist is also indicated by *Ex parte Skinner*, 2 U.S.P.Q. 2d 1788 (Bd. Pat. App. & Int. 1987). In *Skinner*, the Board recognized that there are circumstances in which it is proper to require an applicant to demonstrate that prior art does not inherently anticipate an applicant's invention. Nevertheless, the Board stressed that an Examiner must produce adequate evidence or reasoning to support the Examiner's belief that the prior art inherently anticipates before a *prima facie* case of anticipation is made and the applicant is required to demonstrate lack of anticipation.

> We are mindful that there is a line of cases represented by *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971) which indicates that where an examiner has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, the examiner possesses the authority to require an applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on. Nevertheless, before an applicant can be put to this burdensome task, the examiner must provide some evidence or scientific reasoning to establish the reasonableness of the examiner's belief that the functional limitation is an inherent characteristic of the prior art.

2 U.S.P.Q. 2d at 1789.

In *Skinner*, the Board found that the method of producing the claimed product that was allegedly anticipated by the prior art was relevant to determining whether the Examiner had made a *prima facie* case of anticipation. Since the method of making the prior art product differed significantly from the method of making the claimed product, it was not reasonable to expect that the prior art product had the characteristics of the claimed product.

> Appellant urges that the mold for a contact lens would not reasonably be expected to have a surface roughness of no more than about 12.5 x 10^{-8} meters, RMS. In this regard, we note that appellant's specification indicates that the desired degree of surface smoothness is only achieved by polishing or diamond turning of the surface finish. See page 2, lines 12 through 14. Moreover, appellant utilizes a sputtering technique to apply the chromium onto the mold surface rather than a plating technique as utilized by the reference patent. Absent reasons on the part of the examiner regarding why the natural result of the process used to prepare the mold of Mizutani would have been to achieve the characteristics claimed by appellant's mold, a *prima facie* case of anticipation has not been established.
>
> 2 U.S.P.Q. 2d at 1789.

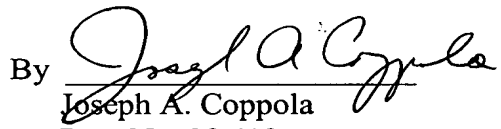
Here, the processes used to prepare atorvastatin by Mills and Roth are significantly different from the processes used to prepare Form V. Thus, according to *Skinner*, there is no *prima facie* case of anticipation based on Mills and Roth.

In view of the above, it is respectfully requested that these rejections be withdrawn.

The time for responding to the Office Action was set for November 3, 2007. Enclosed is a Petition for the Extension of Time under 37 C.F.R. § 1.136(a) for a period sufficient to permit the filing of this response.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with this filing, or any defect seen to be remaining in this application after this filing. The Commissioner is authorized to charge Kenyon & Kenyon's Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

Respectfully submitted,

By 

Dated: February 4, 2008

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PHARMACEUTICAL MANUFACTURING

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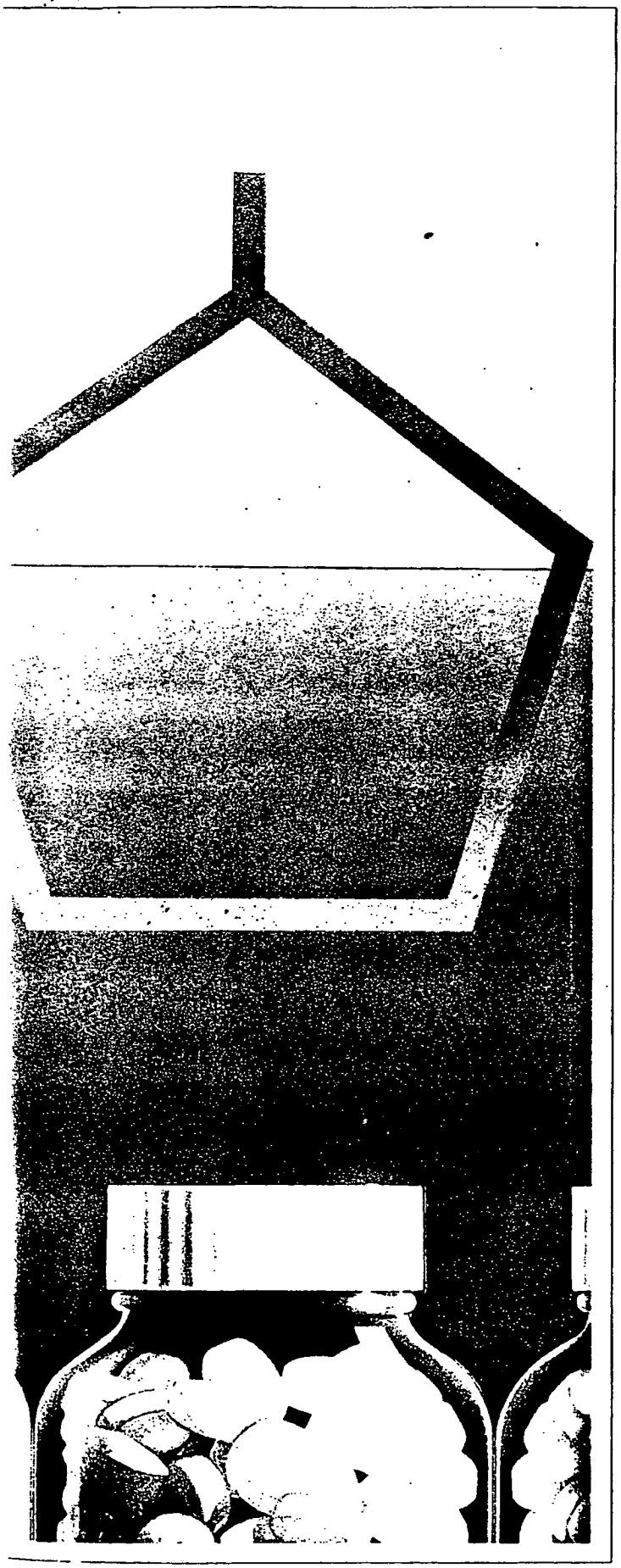


Pharmaceutical Applications of Drug Crystal Studies

G. Michael Wall

Many drugs exist in one or more crystalline forms, either alone or in combination with other drugs, excipients, or solvent molecules. As crystalline configurations vary, lattice energies will also vary, and the different crystal forms may act as if they were different compounds, manifesting differences in melting point, solubility, dissolution rate, density, hardness, and/or chemical stability. Such variations can have serious effects when compounds are used as pharmaceutical agents. For example, a polymorphic drug may change its crystal structure upon compression or grinding during the tabletting process or during scale-up procedures using differing solvent ratios, and the resulting variation could drastically affect the pharmaceutical product's solubility or dissolution rate and, hence, its bioavailability.

The early literature covering pharmaceutically significant aspects of crystal theory contains several excellent reviews,[1-3] including a report on polymorphism in pharmaceutical formulations[2] and a classic review of crystal habits containing specific information on solvates and clathrates.[3] The object of this paper is to provide an overview of the subject and an update on the many recent studies of polymorphism and crystal adducts of commercially available organic drugs.

TERMINOLOGY AND NOMENCLATURE

A pure drug that exhibits more than one crystalline form is known as *polymorphic*, the term *polymorphs* referring to compounds having exactly the same chemical composition. Upon crystallization, however, a crystal may incorporate solvent molecules into its lattice structure, resulting in a crystal adduct called a *solvate*. If the solvent incorporated is water, such a crystal is called a *hydrate*. Obviously, solvates can also exhibit polymorphism; however, solvated and nonsolvated polymorphs of the same compound should be referred to as *pseudopolymorphs* because the crystals of the two types of polymorphs are in fact of different chemical composition. For example, chlordiazepoxide hydrochloride has been shown to exhibit two polymorphic forms and one pseudopolymorphic (monohydrate) form.[4] Cases of polymorphs and solvates constitute the bulk of reports on variations in drug crystals.

Different crystal lattice configurations are associated with different energies, and, for each compound, one configuration will exhibit energy characteristics that render it the most stable. The less-stable (higher-energy) polymorphs are known as *metastable*. In the literature, metastable polymorphs are sometimes also referred to as "unstable." However, the heats of transition of metastable polymorphs can be quite high, resulting in an adequately "stable" form for most practical purposes.

In dealing with stable and metastable polymorphs, two other terms are sometimes encountered: *monotropic* and *enantiotropic*. Expert sources should be consulted for strict definitions.[2,5] For simplicity, however, consider the hypothetical case of two polymorphic pairs, each consisting of a metastable and a stable polymorph. For pair one, heating will cause both polymorphs to pass directly into the liquid phase, but for pair two, upon heating the metastable polymorph will first be transformed into the configuration of the stable polymorph, which will in turn liquefy. The first pair of polymorphs have a monotropic relationship, whereas the second are referred to as enantiotropic. (These hypothetical cases represent ideal situations: in reality, the distinction is often difficult to observe in the laboratory.)

As far as crystal nomenclature is concerned, there is no universally accepted numbering system for polymorphs. The designation of forms 1, 2; I, II; A, B; or α and β does not imply any information on stability or metastability. When a particular solid state is obtained during drug development, it may not be possible to determine whether that form has the lowest possible energy. Therefore, the form designations of a polymorph may indicate the chronological order of discovery, or, if several were discovered simultaneously, may indicate a logical progression in the ascending order of their melting points.

DETECTION METHODS

Several analytical methods are commonly used to study polymorphs, including thermoanalysis, infrared (IR) spectroscopy, and x-ray diffraction. A brief description of each and some applications follow.

Thermoanalysis. The thermoanalytical methods most often used for pharmaceuticals are differential scanning calorimetry (DSC) and differential thermal analysis (DTA). These methods both provide thermograms that illustrate endothermic (heat absorption) or exothermic (heat loss) transitions in solids. The presence of a multiplicity of peaks in a thermogram usually indicates polymorphism.

In DSC, a sample and a reference standard are placed in separate containers, which are gradually heated at a constant rate. As the sample melts, there is a temperature lag behind that of the standard. In order to compensate for this temperature difference, the instrument provides heat input to the sample and records this input, which may be quantitated. Melting usually causes an

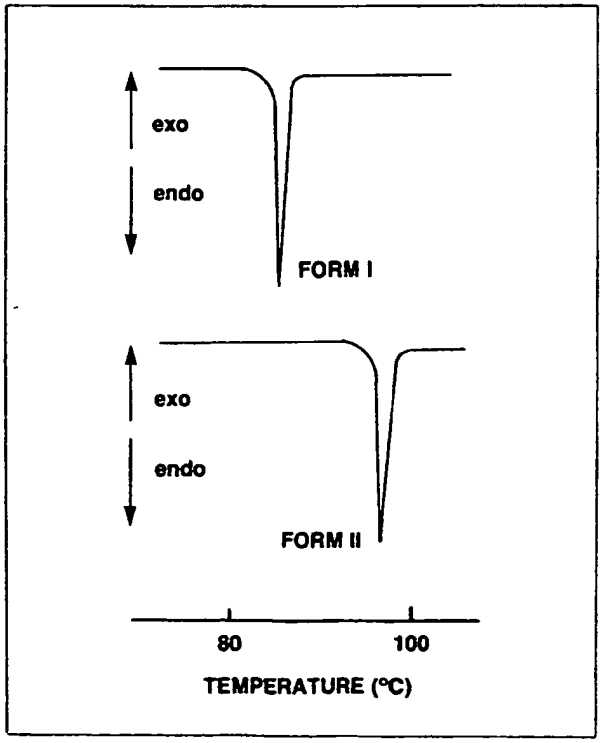
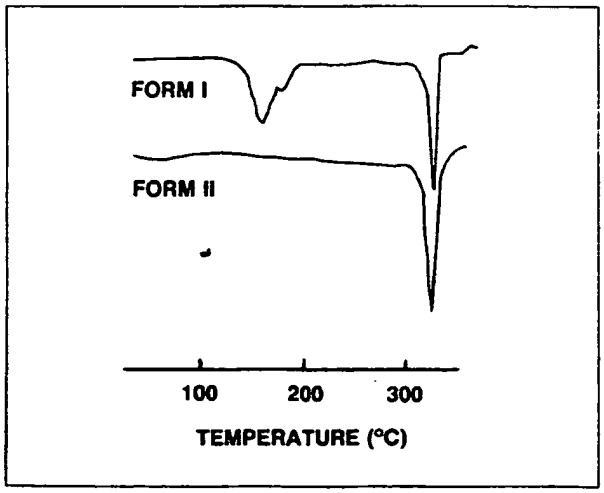


Figure 1: Differential calorimetric scan showing the presence of disopyramide polymorphic forms I and II.

Figure 2: Differential thermograms of commercial (form I) and heat-treated (form II) samples of mercaptopurine.



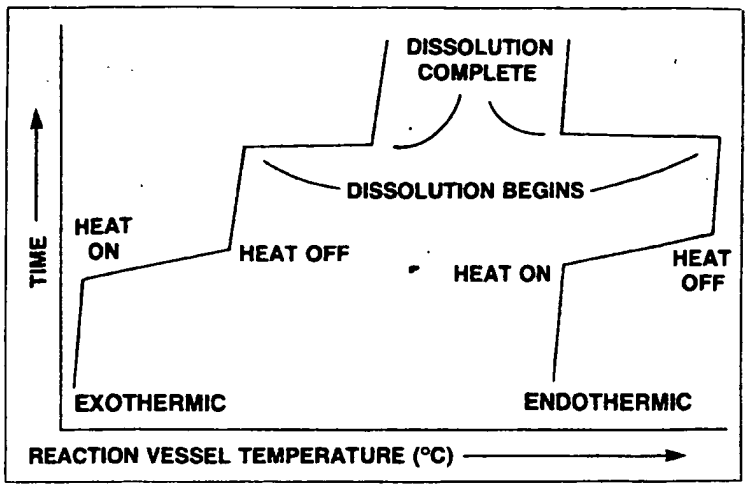
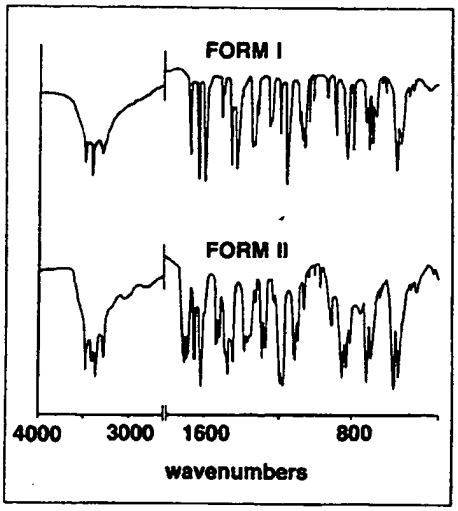


Figure 3: Solution calorimetric thermograms for typical exothermic and endothermic reactions.

Figure 4: Infrared spectra of polymorphic forms I and II of sulfabenzamide.



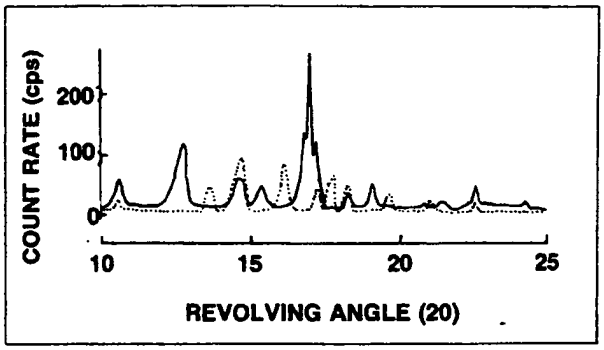


Figure 5: X-ray diffraction patterns for pulverized samples of α and β forms of progesterone. Solid line shows α; dotted line shows β.

endothermic peak in a thermogram. Figure 1 illustrates how DSC was used to identify polymorphic forms I and II of disopyramide; the thermograms' peaks reveal endothermic absorptions at their respective melting points (86° and 97°C).[6]

Differential thermal analysis, also employed in drug crystal studies, is more qualitative than is DSC. In DTA, a sample and reference standard are heated by a common source, and thermocouples placed in contact with them monitor temperature differences, which are plotted against time. DTA has been used to show that commercially available mercaptopurine exists in polymorphic form I—indicated by the two endothermic transitions illustrated in Figure 2—and that incubation of the drug results in a new form (II), which displays only one endothermic transition, also shown in the figure.[7]

In addition to DSC and DTA, solution calorimetry has also been useful in studying polymorphs.[8-10] Since different crystalline or amorphous configurations have different lattice energies, their heats of solution in any given solvent also differ. These heats of solution are measured with a calorimeter connected to a chart recorder. As the drug dissolves in the calorimeter solvent, time-versus-temperature plots are recorded (see Figure 3). This method has been employed to show morphological differences in crystals of β-lactam antibiotics,[8] bendroflumethiazide,[9] indomethacin,[10] and sulfathiazole.[9]

Infrared Spectroscopy. IR spectroscopic evaluation of crystalline compounds is a routine part of most polymorphic studies. The spectra are produced from the solid form as an oil suspension or potassium bromide pellet since solution spectra of polymorphs would look identical. Frequencies of IR absorption correlate closely with vibrations from various parts of the molecule. This technique was useful in identifying tautomeric polymorphs of sulfabenzamide,[11] the spectra of which are shown in Figure 4.

X-ray Diffraction. The most definitive analysis of crystalline-state structure is given by x-ray diffraction studies. Diffraction patterns may be obtained from either a single crystal or a powdered specimen. In single-crystal studies, the x-ray reflection angles off of the rotating crystal are compiled, and interatomic distances, ring planes, and dihedral angles are determined based on these angles. More commonly in polymorphic studies, however, x-ray diffractograms of powdered samples are compared for qualitative differences. For example, this technique was useful in establishing the presence of α and β forms of progesterone in powdered samples (see Figure 5).[12]

Text continued on page 37

RECENT POLYMORPHIC STUDIES

Drug	Number of Polymorphic Forms[a]	References
Acetamide	2	56
Acetaminophen	2	56
Acetohexamide	4(1), 4	57
	4	57
	3	24, 56
	2	58, 59
	NA[b]	60
Acetylsalicylic acid	3	40
	1	61
Amobarbital	NA	62
Amobarbital sodium	1, 1	63
Ampicillin	2, 1	13
Azaperone	2	41, 64
Benactyzine hydrochloride	NA	65
Bendroflumethiazide	2	9
Benperidol	3, 2	66
Betamethazone acetate	NA	67
Betamethazone dipropionate	NA	67
Butabarbital	2	68
Butacaine sulfate	2	16
Caffeine	2	39, 69
Carbromal	1(1)	30
	3	70
Cefamandole naftate	1(2), 1	8
Cefamandole sodium	(2), 2	8
Cefazolin sodium	1(2), 2	8
	1(1)	71
Cephalexin	1, 8	22
	1, 4	72
Cephaloglycin	1, 10	22
Cephalothin sodium	1(1)	8
Chloramphenicol palmitate	4	56, 73
	3	21
	2	74, 75, 76
	1	77
Chlordiazepoxide hydrochloride	2, 1	4
Chloroquine diphosphate	2	78
Chlorothiazide	1(1)	18, 79
Chlorpropamide	5, 1	80
	5	25, 56
	3	39
	NA	61
Cimetidine	3, 1	20
Clotrimazole	2	41
Codeine	3	81
Cyclophosphamide	1, 1	82
Dapsone	NA	83
Difenoxin hydrochloride	2	84
Digitoxin	NA	85
Digoxin	3(1)	86
	3	87
	2 or 3	85
	1(1)	17
Dimethoxanate hydrochloride	NA	88
Diphenadione	NA	88
Diphenidol	NA	65
Dipyridamol	2	39
	NA	65
Disopyramide	2	6, 56
Droperidol	3, 1	66
Erythromycin	1(1), 1	89
Erythromycin estolate	NA	90
Estradiol	1(1)	17
	NA	91
Ethambutol dihydrochloride	NA	83
Ethinyl estradiol	3, 3	92
Ethyl biscoumacetate	2	56
	NA	93
Fluanisone	3	64
Flucloxacillin	1, 2	94
Flufenamic acid	5	56, 95, 96
Glymidine sodium	2	97
Griseofulvin	1, 3	14
	1, 2	13
Homatropine hydrochloride	2	98
Hydrocortisone	1(1)	99
	1	100
Hydroflumethiazide	1(1)	31
Indomethacin	2	10, 35, 101, 102, 103
Maprotiline hydrochloride	3	39
	NA	88
Mebendazole	5	39
Medrogesterone	NA	104
Mefenamic acid	2	56
	NA	95
Menadione	3	56
Meprobamate	3	51, 105
	2	56, 106
Mercaptopurine	2	7
Metahexamide	4, 1	107
	4	56
Methisazone	3	42
Methylprednisolone	2	56
Methyltestosterone	2	108
Metronidazole benzoate	2, 1	109
Nabilone[c]	4(1)	55
Nafcillin	1(1)	71
Nicergoline	2	110
Nicotinamide	3	56
Nifedipine	2	111
Nystatin	2	37
Oxyclozanide	3	56
Penicillamine	2	112
Penicillin G	1(1)	8
Pentobarbital	3	39
	2	113
Phenobarbital	4	56
	2, 1	36
	2(1)	31
	1(1)	30, 32, 43
	NA	62

Drug	Number of Polymorphic Forms[a]	References
Phenobarbital sodium	2	114
Phensuximide	NA	104
Phenylbutazone	5	26
	4	33, 45
	3	27, 28, 56, 115
	2, 2	116
	2	44
Phenylpropylmethylamine hydrochloride	2	56
Phenytoin	2	117
Prednisolone	1, 1	54
Prednisone	1(1)	99
	NA	68
Progesterone	2	12, 56, 118, 119
Propantheline bromide	2	120
Propyphenazone	2	121
Prothioamide	2	56
	NA	104
Rifampicin	NA	122
Spironolactone	4	123
	1(1)	17
Succinylsulfathiazole	2(1), 4	124
Sulfabenzamide	2	11, 39, 125
Sulfaethidole	2	56
Sulfaguanidine	2	56
	NA	50
Sulfameter	5	56
	4, 4	126
	2	38, 127
Sulfamethoxazole	5	128
	3	53
	2(1)	34
	1(1)	52
Sulfamethoxypyridazine	3	56
Sulfanilamide	4	129
	3	47, 56
	NA	48, 130
Sulfapyridine	5	131
	4	56
	3	19
	2(1), 3	132
Sulfathiazole	3(1)	133
	3	56
	2	9, 29, 40, 49
	NA	134
Sulfazamet	2	56
Testosterone	2	108
Tetracaine hydrochloride	3	56
Theophylline	2	56
	NA	135
Tolbutamide	4	23, 56, 136
	3(1)	137
	2	15
	NA	61
Triamcinolone diacetate	2(1)	138
Trimethoprim	3(3)	139, 140
	2	141

[a]Crystal (amorphous), solvate forms.
[b]Evidence of polymorphism noted. Specific number of forms may or may not be available in literature.
[c]Not yet commercially available.

Other Techniques. Traditional methods such as hot-stage microscopy also are still useful in polymorphic studies. Hot-stage microscopy is actually a thermoanalytical technique in which solid-solid transitions are visually observed during melting, cooling, and remelting. Two other methods have been documented to a lesser extent in polymorphic studies: Laser Raman spectroscopy has been employed in the identification of the solvates of griseofulvin,[13,14] and the polymorphs of ampicillin,[13] sulfabenzamide,[11] and tolbutamide;[15] and electron microscopy has been incorporated into polymorphic studies on butacaine sulfate,[16] digoxin,[17] and thiazide diuretics.[18]

Interpretation of polymorphic data is gradually improving from empirical observations to detailed analyses of chemical bonding mechanisms within the crystal. For example, the specific tautomers involved in the conformational polymorphism of sulfabenzamide[11] and sulfapyridine[19] have been determined. As Figure 6 shows, these compounds have the potential to exist as either amides or imides within the crystal. Sulfabenzamide polymorphs exhibit both an amido form (form I) and an amido-imide tautomeric pair (form II);[11] sulfapyridine polymorphs exist only as the imide tautomer.[19] Other sulfonamides reported capable of exhibiting the imido tautomeric form in the crystal are sulfanilamide, sulfamethoxydiazine, sulfadoxine, sulfisoxazole, sulfathiazole, and sulfaguanidine.[19] For the crystalline polymorphs of the H-2 receptor antagonist, cimetidine, the intramolecular distances between the nitrogen atoms of the imidazole ring and the guanidine group have been calculated from x-ray diffraction data.[20] Also, the x-ray crystal analysis of the β-chloramphenicol palmitate polymorph has led to the hypothesis of a model of molecular packing within the crystal.[21]

THE SIGNIFICANCE OF POLYMORPHISM

As mentioned earlier, a change in crystal form could have an impact on the quality and performance of certain drug products. The degree of crystallinity; crystal habit, size, and size distribution; and the state of aggregation of drug particles can all affect bulk properties (e.g., mixing, filling, dusting) and pharmaceutical performance (e.g., dissolution, bioavailability, stability, suspendability, rheology).[22] To highlight the role of polymorphism in setting specifications for raw materials as well as processing parameters, the remainder of this article provides a variety of literature citations and examples.

Effects of Polymorphism on Dissolution Rate and Bioavailability. Dissolution rates of drugs are determined partly by crystal forms. Some polymorphs have identical dissolution rates, while others vary to a great extent. For example, the polymorphic pairs of both disopyramide[6] and mercaptopurine[7] and three of four polymorphs of tolbutamide[23] have been found to have similar dissolution rates, respectively. However, in other studies, polymorphs of acetohexamide,[24] chlorpropamide,[25] and phenylbutazone[26,27] displayed diverse dissolution rates. In a comparative study of the five phenylbutazone polymorphs, form C showed a maximum dissolution rate almost 55% higher than that of form A, while forms B and E displayed about 20 and 35% higher dissolution rates, respectively, than did form A; forms A and D were very similar in rates of dissolution.[26] Since dissolution rates may or may not reflect polymorphic variations, these

data alone should not be used as conclusive evidence of polymorphism.

Crystal formation can be controlled by choice of crystallization solvent or crystallization velocity. Most polymorphic preparations involve recrystallization techniques, but when a spray dryer is used, crystal velocity can be controlled.[28] When the drying temperature of the droplets sprayed from the atomizing nozzle is varied, metastable and amorphous forms (both high-energy because of their greater heats of solution) show greater dissolution rates than does the most stable form, unless there is an extremely rapid conversion to the stable form in the solvent medium.[8,29] Spray drying has been used to produce high-energy polymorphs or amorphous phases of carbromal,[30] chlorothiazide,[18] hydroflumethiazide,[31] phenobarbital,[30-32] phenylbutazone,[28,33] and sulfamethoxazole.[34] Also, freeze-drying has yielded amorphous phases of β-lactam antibiotics.[8]

Because the absorption of many drugs is dependent on their dissolution rates and solubility, polymorphism may be crucial to bioavailability—as classical studies with chloramphenicol have shown.[2,3] Again, however, polymorphism may or may not contribute to variations in absorption. The absorption characteristics of various polymorphs of disopyramide,[6] indomethacin,[35] and phenobarbital[36] have been shown to be very similar, but it has been postulated that variations in the toxicity of the antibiotic nystatin in mice are caused by the differing absorpiton rates of its various polymorphs.[37] (The LD_{50} values of of nystatin suspension used in the study varied between 23.2 and 635.4 mg/kg intraperitoneally, depending on the particular recrystallization technique.) In addition, the rates of absorption of sulfameter forms II and III in humans have been shown to differ (the ratio of form II to form III during the absorption phase was 1:30), although the extent of absorption, as indicated by 72-hour urinary excretion data, did not differ significantly.[38]

Effects of Processing on Crystal Form. Certain processing operations such as milling or compression can trigger a change in a drug product's crystal structure; therefore, it is important to consider the impact of a given processing operation on the crystal form, especially during scale-up. For example, compression studies involving 32 drugs known to exhibit polymorphism revealed that 11 of them were transformed under compression.[39] Specifically, caffeine, maprotiline hydrochloride, and sulfabenzamide all changed, to varying degrees, from unstable to stable polymorphic forms. In the tableting of caffeine, transformation from form A to form B increased drastically (about 20%) to a plateau as the applied pressure was increased (to about 300 MpA).

The heat and stress of the comminution process has been found to induce polymorphic transitions in aspirin,[40] clotrimazole,[41] digoxin,[17] methisazone,[42] phenobarbital,[43] phenylbutazone,[26,27,44,45] sulfamethoxydiazine,[46] sulfanilamide,[47,48] sulfathiazole,[49] and sulfaguanidine.[50]

Another example involves the antiviral agent methisazone, which is used in various formulations as a fine powder and has a tendency to revert to its original "fibrous" crystal form upon storage—a phenomenon that has been referred to as the growth of whiskers. Based on DTA, IR spectroscopy, and x-ray diffraction analysis, the unground and micronized forms have been found to represent two distinct polymorphic forms, the latter of which is the metastable form.[42]

Compression studies with aspirin,[40] meprobamate,[51] phenylbutazone,[44] and sulfathiazole[40,49] have also revealed that certain polymorphic forms are more suited to compression than others. In the case of phenylbutazone, for example, form A has been found to exhibit a higher Brinell hardness number (6.67 MNm^{-2}) than form B (3.63 MNm^{-2}),[44] which indicates form B's relative softness and ease of deformation compared with form A. In addition,

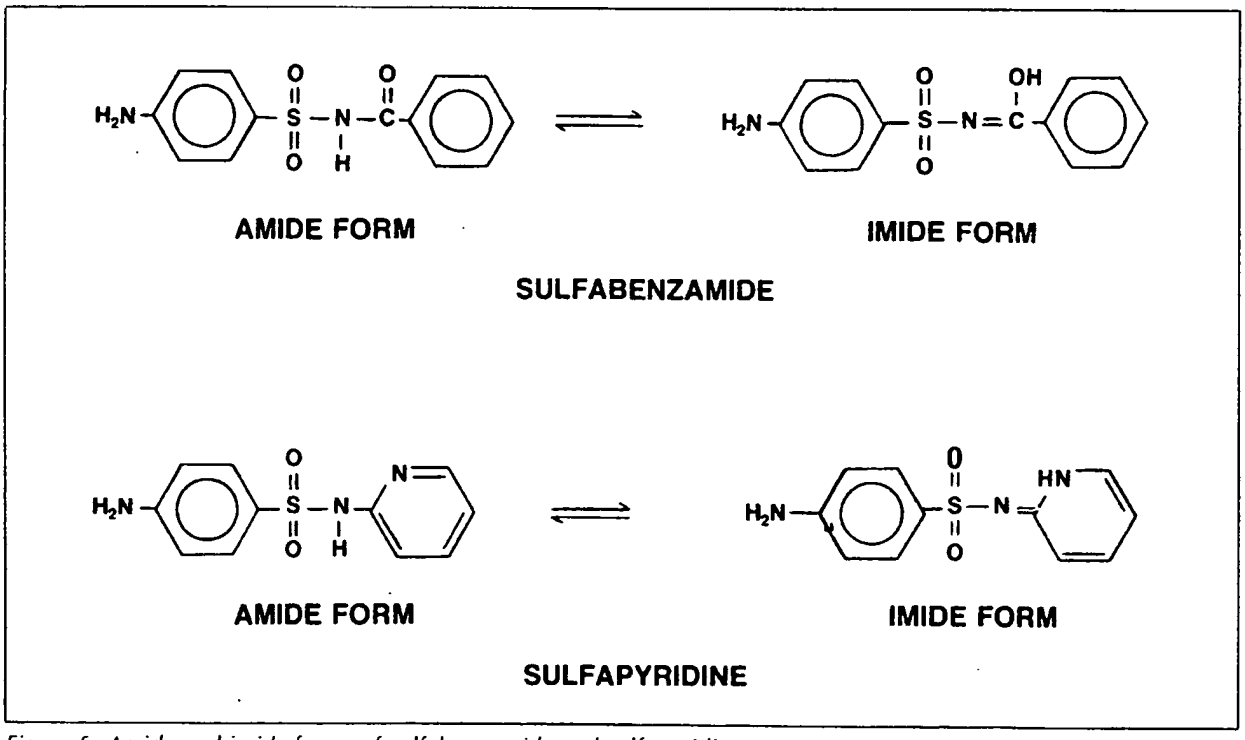


Figure 6: Amide and imide forms of sulfabenzamide and sulfapyridine.

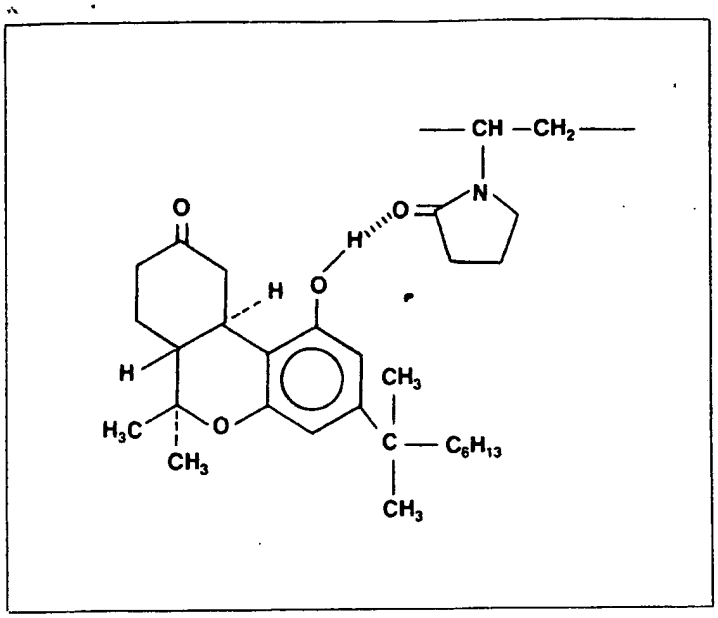


Figure 7: Presumed hydrogen bonding between nabilone, a synthetic cannabinoid, and povidine (PVP).

compression of phenylbutazone disks has been found to produce differences in surface characteristics, which were documented by photomicrography. The more-than-twofold difference in dissolution rates of crystal forms II and IV was attributed to the change in surface characteristics and crystal form.[45]

The Role of Excipients in Polymorphism. Excipients, vehicles, and other additives may have an effect on polymorphic stability; e.g., the transition of sulfamethoxazole to a semihydrate form has been found to be the reason for its instability in aqueous suspensions.[52] When used as additives, methyl cellulose, povidone (polyvinylpyrrolidone or PVP), and sucrose were found to inhibit this transition. On the other hand, carboxymethyl cellulose sodium enhanced the formation of the semihydrate. In other studies cellulose acetate phthalate[34,53] and talc[34] have been found to contribute to the polymorphism of spray-dried, microencapsulated sulfamethoxazole, while colloidal silica[34,53] and montmorillonite clay[34] were discovered to inhibit polymorphism but contribute to amorphism. In addition, it has been found that ointments of prednisolone are stabilized by certain polymorphs of long-chain alcohols, which retard hydrate formation.[54]

Another example of a polymorphic phenomenon in formulation studies involves the synthetic cannabinoid nabilone, an antiemetic.[55] A dry-dosage form of nabilone-starch was found to diminish in activity after several days. Upon extraction and thin-layer chromatographic analysis, however, nabilone was recovered intact. On investigation, it was found that two biologically active polymorphs of nabilone converted to a thermodynamically stable form upon grinding, exposure to heat, or extended storage. When the nabilone was reformulated by dispersion in a water-soluble matrix of PVP, it was found that the PVP-nabilone complex remained in an amorphous state, preventing transition and the resultant loss of activity. Presumably, the phenolic hydroxyl group of nabilone becomes hydrogen bonded to the amide carbonyl of PVP in the matrix as shown in Figure 7, and this bonding prevents the formation of the intermolecular hydrogen bonds necessary for the transition to the less-active crystal form.[55]

Other Polymorphic Studies. The accompanying box presents a compilation of recent polymorphic investigations of organic drugs that are currently on the market. The majority of the studies listed focus on the physicochemical aspects of the polymorphs, although a few stress bioavailability as well as pharmacological efficacy. Earlier literature, which was previously cited, covers the polymorphism of aspirin, chloramphenicol, erythromycin, insulin, meprobamate, novobiocin, and several other anticonvulsants, barbiturates, β-lactam antibiotics, sedatives, steroids, and sulfonamides.[1-3]

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Solid-State Chemistry of Drugs

SECOND EDITION

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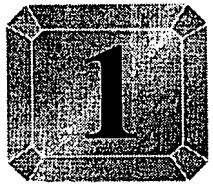


Drugs as Molecular Solids

This chapter provides a general overview of solid-state chemistry of drugs. Specifically, it treats the impact on pharmaceuticals of solid-state chemistry, the crystalline state, amorphous solids, moisture uptake, patents, and physical as well as chemical transformations. In many cases, a subject is introduced in this chapter and addressed in depth in a later chapter. It is hoped that the reader will gain an appreciation of what this discipline encompasses by reading this chapter.

1.1 Role of Solid-State Technology in the Pharmaceutical Industry

Figure 1.1 depicts the central role that solid-state research plays in the pharmaceutical industry. Reflection on the part of anyone even slightly familiar with the industry will confirm many of the connections shown in Figure 1.1, but some specific examples will further point out how important these connections can be in given cases.

Solid pharmaceuticals exist as **polymorphs**, **solvates**, or in **amorphous** forms, collectively described as **solid forms**. Figure 1.2 shows the solubility behavior of two polymorphs with time. It is clear that the solubility of each of the solid forms is decreasing because of the crystallization of a more stable crystal form (Carless *et al.*, 1968). Thus, this figure illustrates the effect of polymorphic change on **suspension** stability. Obviously these changes reflect on the stability of the product as well as

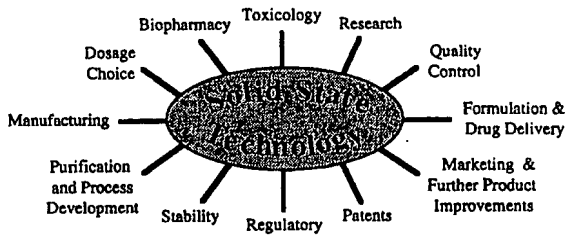


Figure 1.1 A diagram of the role of solid-state studies in the pharmaceutical industry.

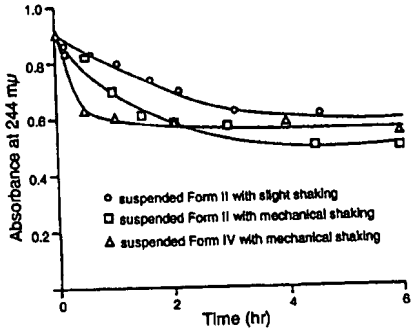


Figure 1.2 Decrease in absorbance of a cortisone acetate Form II solution in the presence of suspended Form II or Form IV as a function of time (Carless *et al.*, 1968).

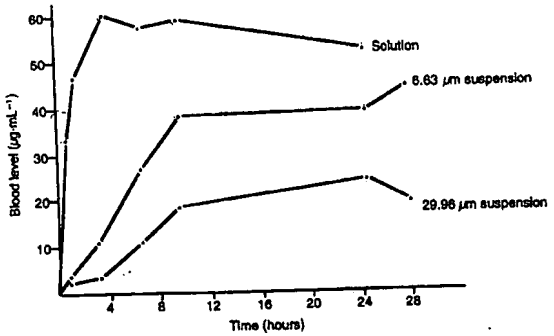
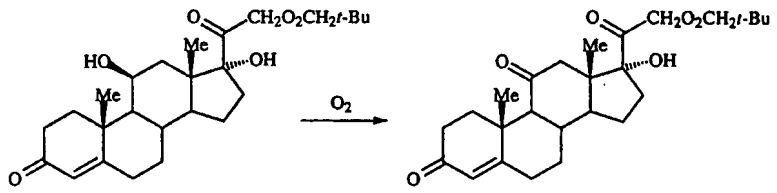


Figure 1.3 Blood levels of phenobarbitone versus time after intramuscular injection of two preparations with different particle sizes (redrawn from Miller and Pincher 1971).

regulatory issues, quality control, **formulation**, and drug bioavailability. Figure 1.3 depicts the effect of particle size on the **dissolution rate** of phenobarbitone and illustrates the role of solid-state technology in the formulation and **drug delivery**, quality control, and regulatory areas.

Studies of hydrocortisone *tert*-butylacetate and prednisolone *tert*-butylacetate (Byrn *et al.*, 1988; Lin *et al.*, 1982) and dihydrophenylalanine (Ressler, 1972) show that different crystal forms of these substances have different chemical reactivity. For example, the hexagonal crystal form of both hydrocortisone *tert*-butylacetate and prednisolone *tert*-butylacetate oxidizes in the solid state whereas the other crystal forms of these two pharmaceuticals are chemically stable.

The shape and particle size of the solid drug substance can have an important effect on the **flowability**, **syringeability**, **filterability**, **tableting behavior**, and **bulk density** of the drug. For example a suspension of plate-shaped crystals may be injected through a small needle with greater ease than one of needle-shaped crystals. Similarly, the tableting behavior of plate-shaped crystals would differ from that of needle-shaped crystals. Furthermore, the shape and size of the particles is generally related to the internal crystal structure of the solid. Thus, the internal structure of the solid material can dramatically influence the bulk properties of the drug. These properties in turn relate to formulation, manufacturing, patents, quality control, regulatory, and possibly other areas indicated in Figure 1.1.



hydrocortisone 21-*tert*-butylacetate **cortisone 21-*tert*-butylacetate**

1.2 THE CRYSTALLINE STATE: BASIC CONCEPTS

An understanding of the solid-state chemistry of drugs begins with a statement of several general points:

- most drugs are used in a crystalline form
- crystals are held together by molecular forces
- the arrangement of molecules in a crystal determine its physical properties
- the physical properties of a drug can affect its performance

We can then proceed to learn how an understanding of the crystalline state leads to understanding of drug properties. (A treatment of non-crystalline, or amorphous, solids is given in Chapter 12.)

To accommodate the general reader in following this discussion of the crystalline state, brief definitions of some terms are listed in a glossary at the end of the book. Many of the terms may require further explanations which will be given when appropriate.

A. PACKING AND SYMMETRY

One definition of a crystal is that of a solid in which the component molecules are arranged, or "packed," in a highly ordered fashion. When the specific local order, defined by the **unit cell**, is rigorously preserved without interruption throughout the boundaries of a given particle, that particle is called a **single crystal**. This ordered packing leads to a structure with very little **void space**, which explains why most substances are more dense in their solid state than in their liquid state. By way of illustration, Figure 1.4 shows a projection of a unit cell and also shows how tightly the molecules are packed in a typical crystalline substance such as glycine.

Looking at this example and contemplating the enormous number of crystalline compounds known to modern science, not to mention those to be discovered, it be-

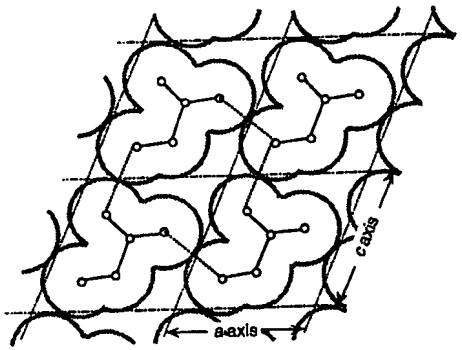


Figure 1.4 A close packed layer of glycine molecules in a crystal projected on the *ac* plane. The heavy gray lines show the van der Waals radii of the atoms (the hydrogens have been omitted for clarity).

comes obvious there must be a remarkable variety of structures found in different crystals. What factors, then, determine the crystal structure of a given compound?

When the question "In how many different ways can varied-shaped molecules be packed?" is put on a mathematical basis, it has been shown that certain **symmetry elements** (or, **symmetry operations**) are involved and that all possible combinations of these can be summarized in exactly 230 ways, called **space groups**. The symmetry operations are listed in Table 1.1. Formal representations of the 230 space groups, which encompass all seven **crystal systems** and all possible combinations of symmetry operations, are found in the *International Tables for Crystallography* (1987).

To understand how the packing of a crystal structure is described by the symmetry operations of the space group it may be helpful to regard the following example (see Figure 1.5). Figure 1.5 shows a diagram of the symmetry elements in space group *Pmm*2. The *P* means that the space group is **primitive** rather than **body-centered** or **face-centered**. The *mm*2 means that the cell contains **mirror planes** (*m*) perpendicular to both the *a* and *b* axes and a **two-fold rotation axis** along the *c* axis.

Table 1.1 The Symmetry Elements of Crystal Packing[a]

Symmetry Element	Description
rotation axis	When a rotation of 360°/*n* results in the same structure, then the crystal contains an *n*-fold rotation axis. For crystals, *n* is restricted to 1, 2, 3, 4, and 6.
screw axis	An *n*-fold screw axis exists when a rotation of 360°/*n* followed by a translation parallel to the axis of rotation brings the structure into coincidence.
rotatory-inversion axis	An *n*-fold rotatory-inversion axis exists when a rotation of 360°/*n* followed by inversion results in the same structure.
mirror plane	A mirror plane exists when a reflection through that plane results in the same structure.
glide plane	A glide plane exists when reflection through a mirror plane followed by translation brings the structure into coincidence.

a Note that a crystal containing only one enantiomer of a chiral compound cannot fall into a space group containing any one of the last three symmetry elements in Table 1.1.

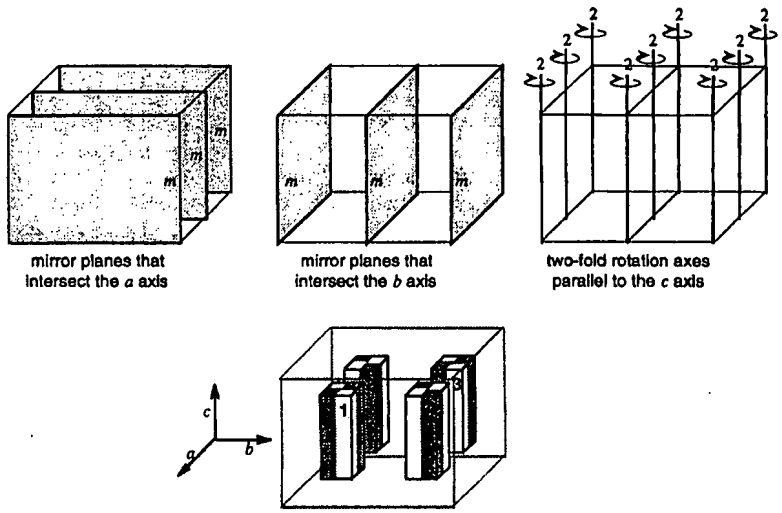


Figure 1.5 Symmetry elements for space group *Pmm*2.

Taking block 1 at position (x,y,z) and reflecting it across the mirror that intersects the *a* axis at $\frac{1}{2}a$, block 2 is obtained. Reflecting block 2 across the mirror that intersects the *b* axis at $\frac{1}{2}b$ generates block 3, and block 4 results from block 3 being reflected across the mirror at $\frac{1}{2}a$. [In actual cases, of course, these blocks are molecules, but the operations are the same and thus the *x*, *y*, *z* coordinates of each atom in molecule 1 are translated to the corresponding $(1-x,y,z)$ in the first step, to $(1-x,1-y,z)$ in the next step, and $(x,1-y,z)$ in the last step.] Note that this combination of mirror planes necessarily creates the two-fold rotation axes parallel to the *c* axis. These steps, in any order, are continued into the neighboring unit cells. In this exercise we are, in a sense, mimicking actual crystal growth.

B. Forces Responsible for Crystal Packing

At this point, it is appropriate to consider the forces responsible for holding crystals together. **Ionic crystals** are held together by **ionic bonds** while **organic crystals** are held together largely by **non-covalent interactions**. These non-covalent interactions are either hydrogen-bonding or **non-covalent attractive forces**. Both hydrogen-bonding and non-covalent attractive interactions result in the formation of a regular arrangement of molecules in the crystal. **Non-covalent attractive interactions**, which are sometimes called **non-bonded interactions**, depend on the dipole moments, polarizability, and electronic distribution of the molecules. Hydrogen bonding, of course, requires donor and acceptor functional groups. Another important factor is the symmetry of the molecules. Kitaigorodskii (1961) provided a review of the forces holding crystals together in his classic book *Organic Chemical Crystallography*. The two-

volume *Structure Correlations* (Bürgi and Dunitz, 1994) describes in detail the modern view of crystal packing.

The symmetry (or lack of symmetry) of a molecule determines how it is packed in the crystal and, in some cases, determines the overall symmetry of the crystal. Molecules with symmetries that allow them to fit together in a close-packed arrangement generally form better crystals and crystallize more easily than irregular molecules. This factor is not always evident from molecular models.

Several researchers have described crystal packing forces in specific classes of compounds. Reutzel and Etter (1992) evaluated the conformational, hydrogen-bonding, and crystal-packing forces of acyclic imides. Crystal-packing forces in biphenyl fragments were evaluated by Brock and Minton (1989); Gavezzotti and Desiraju (1988) have analyzed packing energies and packing parameters for fused-ring aromatic hydrocarbons.

Kitaigorodskii (1961) has advanced the **close-packing theory** to explain the forces holding crystals together. He suggested that the basic factor that affects free energy is the packing density which affects ΔH, enthalpy. The denser or more closely packed crystal has the smaller free energy. This means that the heat of sublimation (and, to a first approximation, melting point) increases as the packing density increases and, that in a series of polymorphs, the densest polymorph is the most stable. This is the molecular basis of the **density rule** which states that if one modification of a molecular crystal has a lower density than the other, it may be assumed to be less stable at absolute zero (Burger and Ramberger, 1979a). However, it is important to note that there are exceptions to this rule. Some exceptions probably arise because strong hydrogen bonds can negate less dense packing (*e.g.*, ice) thereby causing the less dense polymorph to be more thermodynamically more stable (Burger and Ramberger, 1979a–b). Brock *et al.*(1991) studied the validity of **Wallach's rule**, which states that the racemic crystals of a pair of enantiomers are denser and thus more stable than crystals of the individual enantiomers, and showed that, for the 65 chiral/racemic pairs investigated, the racemic crystals are only ~1% more dense than the corresponding chiral crystals (yet the racemates are less dense for many individual pairs).

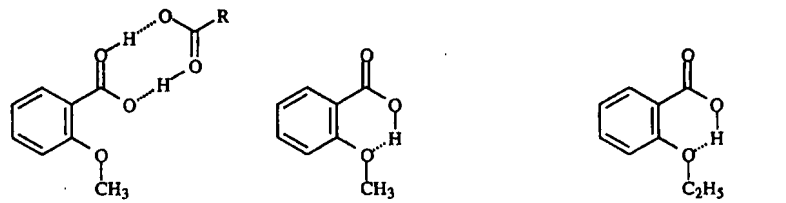
Kitaigorodskii (1961) also pointed out the importance of symmetry which affects ΔS, entropy. The free energy of a crystal undoubtedly increases as the number of crystallographically **independent molecules** in the crystal increases. Thus high symmetry, which reduces the number of independent molecules in a crystal, *increases* the free energy of the crystal and conflicts with the *reduction* in free energy gained from close packing. The magnitude of these opposing effects varies from structure to structure.

C. Hydrogen Bonding

Of the various forces that hold organic molecules in the solid, hydrogen bonding is perhaps the most important. Etter (1990) has reviewed the extent and types of hydrogen bonding that can exist in solids and pointed out that polar organic molecules in solution tend to form hydrogen-bonded aggregates. These aggregates are precursors to the crystals which form when the solution is supersaturated. This concept helps to explain the many different hydrogen-bonding motifs seen in different solids.

Several different types of carboxylic acids have been studied. For example, in *o*-alkoxybenzoic acids, the presence of dimers or the formation of intramolecular hydrogen bonds depends on the state of the sample. In *o*-anisic acid, dimers are observed in

the solid state while intramolecular hydrogen bonds are observed in dilute solution. However, in *o*-ethoxybenzoic acid, only intramolecular hydrogen bonds are observed in both the solid state and in solution (Etter, 1990).

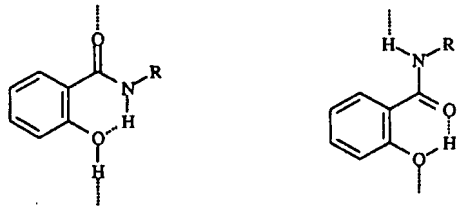


o-methoxybenzoic acid
in the solid state

o-methoxybenzoic acid
in solution

o-ethoxybenzoic acid
in solution and in the solid state

Etter *et al.* (1988) also studied the hydrogen bonding in salicylamide derivatives and pointed out that two types of hydrogen bonding patterns are possible in these compounds. One pattern involves an intramolecular —N—H···OH— hydrogen bond and an intermolecular —O—H···O=C hydrogen bond while the other pattern involves an intermolecular —N—H···OH— hydrogen bond and an intramolecular —O—H···O=C hydrogen bond.



Intra: NH···OH
Inter: C=O···HO

Intra: C=O···HO
Inter: NH···OH

Etter and co-workers (1990a) defined a system which uses a graph set to classify and symbolically represent the different types of hydrogen bonds that can be formed. A short representation of the different graph sets is shown in Figure 1.6. A graph set motif designator (C for intermolecular chains or **catemers**, R for intermolecular rings, D for discrete or other finite sets, and S for intramolecular hydrogen bonds) is assigned by identifying the size or degree of the hydrogen-bond pattern G, the number of acceptors a, the number of donors d, and the total number of atoms n in that pattern. This designation takes the form: $G_d^a(n)$.

Etter (1990b) also developed rules governing hydrogen bonding in solid organic compounds. Hydrogen-bond donors and acceptors in solids are classified either as "reliable" or "occasional" donors and acceptors and are listed in Table 1.2. Using these classifications, three rules were devised:

1. All reliable proton donors and acceptors are used in hydrogen bonding.
2. Six-membered ring *intra*molecular hydrogen bonds form in preference to *inter*molecular hydrogen bonds.

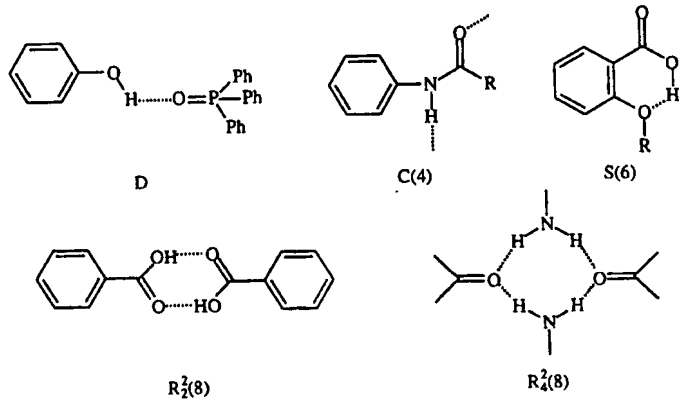


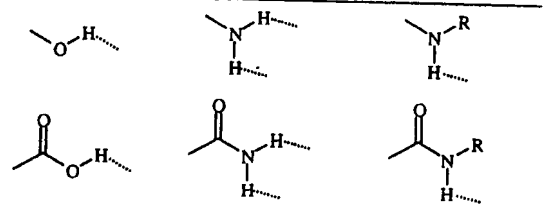
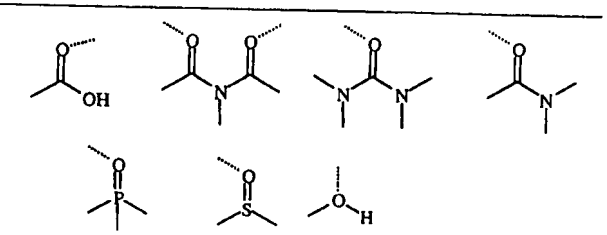
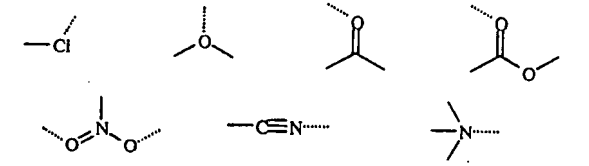
Figure 1.6 Etter graph sets describing different hydrogen bond motifs where D designates a discrete or other finite set, C a chain or catemer, S an intramolecular ring, and R designates an intermolecular ring. The number of hydrogen-bond acceptors in rings is superscripted, the number of hydrogen-bond donors is subscripted, and the total number of atoms in the hydrogen-bond pattern is in parentheses (Etter, 1990; Bernstein *et al.*, 1995).

3. The best proton donors and acceptors remaining after intramolecular hydrogen bond formation will form intermolecular hydrogen bonds.

These rules apply quite well to hydrogen bonding of small molecules. However, in some larger molecules (*e.g.*, erythromycins), factors dictated by the geometry of the molecule as well as the large number of donors and acceptors present may make it impossible to satisfy all these rules.

It has been demonstrated that the systematic study of **cocrystals** (crystals which contain an ordered arrangement of two different neutral molecules that are not solvent molecules) can lead to insight concerning the factors influencing hydrogen bonding in crystals (Etter and Baures, 1988; Etter *et al.*, 1990a–b; Etter and Adsmond, 1990; Etter and Reutzel, 1991). An important aspect of this research into hydrogen bonding is the realization that cocrystals can form and crystallize from certain solutions that contain more than one molecular species. Cocrystals are often formed between hydrogen-bond donor molecules and hydrogen-bond acceptor molecules. The geometry and nature of hydrogen bonding in cocrystals can be described using the above rules. Among the cocrystals studied by Etter's group were cocrystals involving ureas with ketones, carboxylic acids with 2-aminopyridine (see Figure 1.7), as well as adenine or cytosine with many acidic organic compounds including carboxylic and *N*-acyl-amino acids. The urea cocrystals are especially interesting because so many can be studied. Other cocrystal systems investigated by Etter's group include:

Table 1.2 Reliable and Occasional Hydrogen Bond Donors and Acceptors

Type	Functional Group Involved
Reliable Donor	
Occasional Donor	
Reliable Acceptors	
Occasional Acceptors	

Etter, 1990; Bernstein *et al.*, 1995

pyrimidines, pyridines ..... carboxylic acids
pyridine-*N*-oxides ..... acids, alcohols, amines
triphenylphosphine oxides ..... acids, amides, alcohols, ureas, sulfonamides, amines, water
carboxylic acids ..... other carboxylic acids, amides
m-dinitrophenylureas ..... acids, ethers, phosphine oxides, sulfoxides, nitroanilines
imides ..... other imides, amides

The formation of cocrystals may also be important in explaining certain drug-excipient interactions.

Panunto *et al.* (1987) have reviewed hydrogen bond formation in crystalline nitroanilines. They showed that hydrogen bonding occurred between the amino group and the nitro group even though the nitro group is only an occasional acceptor. In general, they found that the donor hydrogen from the amino group is placed equidistant

between the acceptor oxygens of the nitro group. The geometry of this interaction appears to be controlled by the lone pair directionality of the nitro groups.

This elegant work by Etter on graph set definitions and qualitative hydrogen-bonding rules can greatly assist the understanding of the interaction of molecules in the solid state and presumably also in solution. Further discussion of hydrogen bonding in salts is included in Chapter 5.

1.3 A Given Substance can Crystallize in Different Ways

Apart from exhibiting differences in size, crystals of a substance from different sources can vary greatly in their shape. Typical particles in different samples may resemble, for example, needles, rods, plates, prisms, etc. Such differences in shape are collectively referred to as differences in **morphology**. This term merely acknowledges the fact of different shapes: it does not distinguish among the many possible reasons for the different shapes.

Naturally, when different compounds are involved, different crystal shapes would be expected as a matter of course. When batches of the *same substance* display crystals with different morphology, however, further work is needed to determine whether the different shapes are indicative of polymorphs, solvates or just **habits**. Because these distinctions can have a profound impact on drug performance, their careful definition is very important to our discourse. At this time, only brief definitions are presented, but an exhaustive treatment of each will be given later.

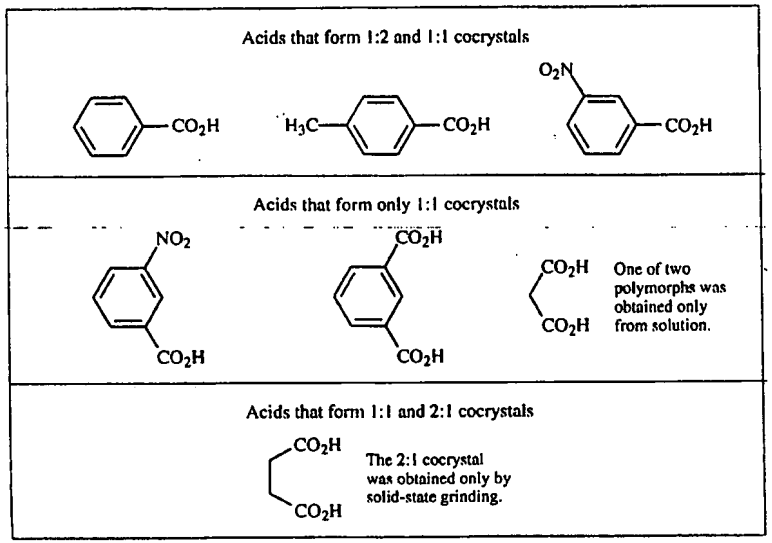


Figure 1.7 Observed stoichiometries of cocrystals of 2-aminopyridine with the compounds listed here (Etter and Adsmond, 1990).

Polymorphs — When two crystals have the *same chemical composition* but *different internal structure* (molecular packing) they are polymorphic modifications, or polymorphs. (Think of the three forms of carbon: diamond, graphite, and fullerenes.)

Solvates — These crystal forms, in addition to containing molecules of the same given substance, also contain *molecules of solvent* regularly incorporated into a unique structure. (Think of wet, setting plaster: $CaSO_4 + 2\,H_2O \rightarrow CaSO_4{\cdot}2H_2O$)

Habits — Crystals are said to have different habits when samples have the *same* chemical composition and the *same* crystal structure (*i.e.*, the same polymorph and unit cell) but display different shapes. (Think of snowflakes.)

Together, these solid-state modifications of a compound are referred to as **crystalline forms**. When differences between early batches of a substance are found by microscopic examination, for example, a reference to "form" is particularly useful in the absence of information that allows the more accurate description of a given variant batch (*i.e.*, polymorph, solvate, habit, or amorphous material). The term **pseudopolymorphism** is applied frequently to designate solvates.

To put these important definitions into a practical context, let us look at two cases in which a drug was crystallized from several different solvents and different-shaped crystals resulted in each experiment. (See Figures 1.8 and 1.9.)

Although sometimes dramatically different shapes were obtained upon changing solvents for the various crystallizations, the final interpretations in the two cases were significantly different. Figures 1.8 and 1.9 can be used to illustrate the application of the terminology defined in the previous paragraphs. Upon first seeing these pictures, it might be asked: "Although each of these drugs shows different *morphology* with different treatment, are the different-shaped crystals *polymorphs*, *solvates* or merely different *habits*?" After various investigations (*cf.* Methods, Chapter 2) it was concluded that all *forms* of the aspirin (Figure 1.8) have the same *structure* and therefore each is a different *habit* of the aspirin crystal. The various crystals of β-estradiol, however, were found to exist as a number of *solvate* forms (two *unsolvated* forms are also known but not shown in Figure 1.9). At this point we are aware that: a given structure can form crystals of quite different shapes; and a given drug may exist in more-than-one crystal structure or crystal form (*i.e.*, polymorph or solvate).

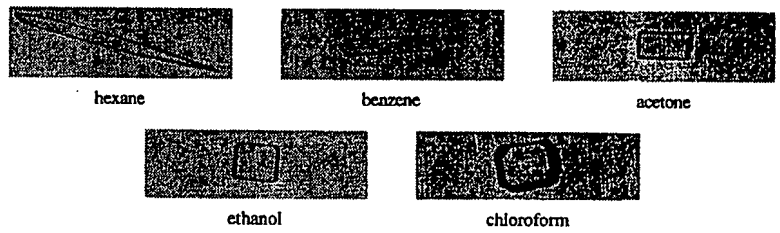


Figure 1.8 Aspirin crystals grown from different solvents.

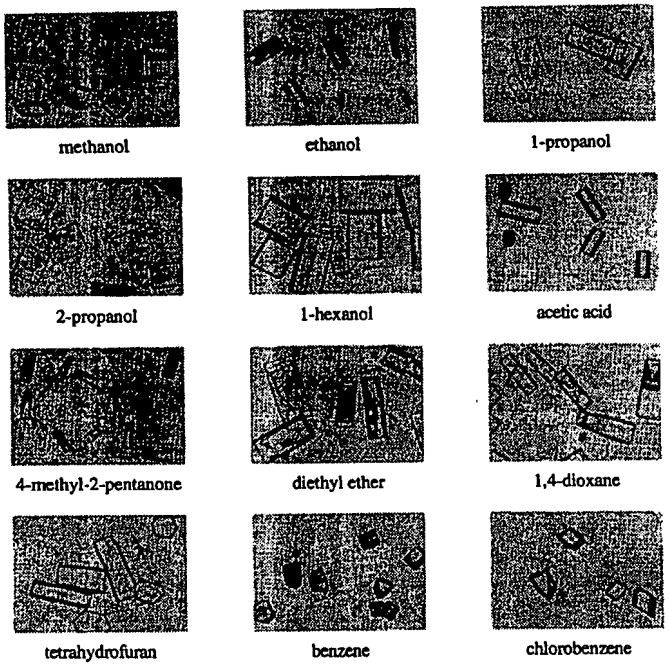


Figure 1.9 β-Estradiol pseudopolymorph crystals (solvate and crystallizing solvent are indicated, Kuhnert-Brandstätter, 1971).

1.4 PROPERTIES THAT AFFECT PHARMACEUTICAL BEHAVIOR

The familiar example of pure carbon in its three forms—diamond (tetrahedral lattice), graphite (polyaromatic sheets), and fullerenes (polyaromatic spheres)—dramatizes the profound effect that differences in crystal structure can have on the properties of a solid. Similar effects can apply to other solid compounds, including drugs. The complex nature of manufacturing operations and regulatory requirements peculiar to the pharmaceutical industry thus demands an even closer look at how the properties of a given drug can vary with each of its solid-state forms. Given the endless chemical variety of modern drug molecules it becomes obvious why solid-state studies are vital to the thorough characterization of pharmaceuticals.

Many physicochemical properties of a drug (see Table 1.3) vary when the solid-state *structure* of the substance is altered. The *practical significance* of any of these differences will, of course, vary from case to case.

Other properties of drug crystals that are of concern primarily in pharmaceutical *operations* also need to be addressed. These are properties that vary even when the crystal structure is fixed and are directly or indirectly related to surface relationships and thus largely controlled by **crystal habit** and **size distribution** (see Table 1.4). These

Table 1.3 Properties of a Compound that Depend on Structure Differences

Density	Water Uptake	Solid-State Reactivity
Hardness	Optical Properties	Physical Stability
Cleavage	Electrical Properties	Chemical Stability
Solubility	Thermoanalytical Behavior	

Table 1.4 Some Areas Where Control of Solid Form and Size Distribution are Important

Yield	Milling	Dissolution
Filtration	Mixing	Suspension Formulation
Washing	Tableting	Lyophilization
Drying	Flowability	

variables determine how particles behave with respect to neighboring particles (and upon exposure to solvent or solvent vapor) and thus the physical properties of powders.

At this point, the concept that these crystal properties are directional is introduced. In discussing symmetry and space groups (see Sec. 1.2A), it is important to convey the notion that unit cells contain different symmetry elements along their axes. A necessary consequence of this fact is that *most drug crystals have different properties in different directions*, or alternatively stated, *the chemistry on the different faces of a drug crystal may be quite different*. Both the structure and the properties, in short, are **anisotropic**. For example, one face of a crystal may be studded with carboxyl groups whereas another face might be entirely occupied by phenyl moieties, thus giving rise to some relatively hydrophilic surfaces and some hydrophobic surfaces, to mention only one consequence. Furthermore, with a change in crystal habit, the relative areas, hence the relative chemical importance of these two kinds of faces would be altered. If we now consider additional crystal forms of the same compound, the anisotropic chemical variability must be regarded anew for each polymorph and solvate.

Although it is by now obvious that control of crystal formation is of extreme importance, this control is not always easy to achieve. What general principles dictate the formation of crystals?

1.5 HOW CRYSTALS FORM

In this section we discuss how crystals form and the factors that influence crystallization. Table 1.5 lists the common crystallization methods employed for pharmaceuticals. Most of the methods covered in Table 1.5 depend on reducing the **solubility** of the compound by one means or another. It is therefore necessary to carefully define the solubility-related terms that will be used repeatedly in the discussions that follow.

A. SOLUBILITY

The solubility of a solid substance is the concentration at which the solution phase is *in equilibrium with a given solid phase at a stated temperature and pressure*. Under these conditions the solid is neither dissolving nor continuing to crystallize. Note that the definition implies the presence of a specific solid phase. Once determined under the

Table 1.5 Common Methods for the Production of Solids in the Pharmaceutical Industry

Evaporation (including spray drying and slurry fill)
Cooling a solution
Seeding a supersaturated solution with crystals of the desired form
Freeze drying (including from mixed solvents)
Addition of antisolvents
Salting out
Changing pH
Addition of reagent to produce a salt or new compound
Deliberate phase transitions during slurry, washing or drying steps
Simultaneous addition of two solutions

stated conditions, however, we can talk about the "solubility" of a given phase (*e.g.*, a specific polymorph or pseudopolymorph) as a quantity, even in the absence of that solid phase.

Use of the term "equilibrium" in connection with crystallizing systems requires clarification. When a substance exists in more than one crystal form, that is, when other polymorphs are possible, only the *least soluble* of these at a *given* temperature is considered the most physically stable form at that temperature, all others are considered to be **metastable forms**. In given cases, a solution of a substance may be in apparent equilibrium with one of these metastable phases for a long time, in which case, the system is in metastable equilibrium and is expressing the thermodynamic solubility of *that* solid form.

It is important to stress the difference between polymorphs and solvates (pseudopolymorphs) at this point. If a pseudopolymorph exists, it is always (with few exceptions) the most stable form in the solvent that produces the pseudopolymorph.

Undersaturation pertains to solutions at a lower concentration than the saturation value (*i.e.*, diluted solutions). *Crystals will dissolve in undersaturated solutions.*

Saturation is the state of a system where *the solid is in equilibrium with the solution*, or in other words, *the solution will neither dissolve crystals nor let them grow* (*i.e.*, the concentration of the solution represents the solubility value for that crystalline phase).

Supersaturation pertains to solutions that, for one reason or another (*e.g.*, rapid cooling of a saturated solution without forming crystals) are at a higher concentration than the saturation value. *Supersaturation is required for crystals to grow.*

B. Nucleation

Supersaturated solutions can sometimes remain in that condition for long periods without forming crystals. For example, the reader may have heard of slowly cooling very clean water to well below its freezing point of 0 °C without the formation of ice crystals taking place. The first step in forming crystals from a supersaturated solution requires the assembly of a critical number of ordered molecules (unit cells) into viable **nuclei**. This process is termed **primary nucleation**. Assemblies below the critical number tend to dissolve while those above the critical number persist and grow into recognizable crystals. This behavior is based on the simple fact that the surface area of a spherical body increases with the square of its radius but the volume increases with the cube

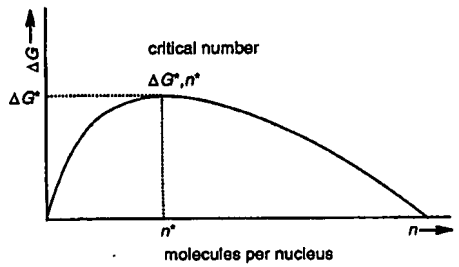


Figure 1.10 Free energy changes (ΔG) which occur during nucleation. Molecules assemble and disassemble until a nucleus of a critical number with an energy ΔG^* is achieved; then crystallization ensues as the size of the nucleus increases (Lieser, 1969).

of the radius. In other words, as an assembly becomes larger, the internal bonds holding it together become relatively more significant than the surface forces (solvent-solute interactions) acting to pull the particle apart. A more formal explanation of this phenomenon is given in Figure 1.10.

Despite various tidy theoretical analyses of nucleus formation that have been derived, nucleation in the laboratory or industrial setting remains very difficult to control in perhaps the majority of cases, due to the many disparate factors that are observed to affect nucleation (Table 1.6). In addition to primary nucleation, there is a phenomenon known as **secondary nucleation** which involves further crystallization after initial crystals are formed (either from deliberate seeding or primary nucleation). Among the factors which affect secondary nucleation are: agitation (including the design and type of crystallization vessel and agitator); temperature and concentration gradients; friable (breakable) crystal form or habit; and crystal irregularities caused by impurities. Secondary nucleation sometimes has undesirable consequences since it tends to produce excessive numbers of very small particles. Furthermore, once crystallization begins, factors like concentration, supersaturation, and many of the parameters in Table 1.6 may change, producing a dynamic environment that makes continued control of the process exceedingly difficult.

The most important lesson in this discussion is that *the number of particles and the crystal form resulting from a crystallization procedure are determined by nucleation*

Table 1.6 Factors that may Initiate Nucleation

Pre-existing nuclei on equipment or in air
Foreign particles of a suitable nature
Deliberate seeding with desired phase
Local hypersaturation by soluble metastable phase
Separation of a liquid phase during processing (*e.g.*, a temperature change or addition of antisolvent)
Local hypersaturation at an immiscible solvent interface
Ultrasonic or shock waves
Scratched surfaces
Local temperature irregularities
Local concentration gradients (*e.g.*, created by surface evaporation or reagent addition)

events. Thus: "one nucleus, one large crystal; a billion nuclei, a billion tiny crystals." In polymorphic systems nuclei of different structures can form and coexist in a given crystallization, in which case a mixture of crystal forms may be found in the final product when kinetic factors prevent achievement of equilibrium.

Consider the situations shown in Figure 1.11. In the top two panels, a crystallization procedure, using apparently the same protocol, affords different polymorphs on separate occasions (needles and plates). In the bottom panel, the "same procedure" results in a mixture of the polymorphs. In these cases, lack of control of the nucleation process leads to lack of control of the polymorphs present. It is therefore common practice to add nuclei of the desired phase deliberately at an appropriate stage in an industrial crystallization. This process is called **seeding**, and is one of many measures used to control the outcome of crystallizations.

C. Transitions Between Crystal Forms

When different crystal forms are possible for a substance each form has a solubility value under a fixed set of conditions: solvent composition; temperature; and pressure. Even if crystals of two forms have been produced, however, the system will always

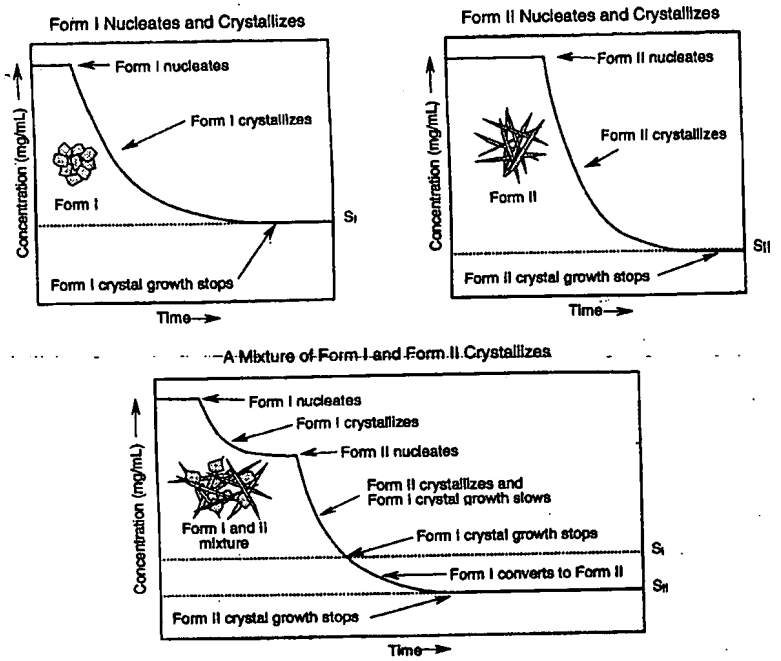


Figure 1.11 Uncontrolled crystallization in a polymorphic system showing the different polymorphs (top panels) or the mixture of polymorphs (bottom panel) which can result. (SI and SII are the solubility limits for Forms I and II, respectively.)

tend to produce only the less soluble of two forms eventually (see Figure 1.11). To be sure, the time it takes to express this tendency depends on kinetic factors and may be quite variable; but in any event, a less soluble form never converts to the more soluble form under rigorously defined conditions.

A few illustrations of the dissolution behavior of some polymorphic drugs may help to review these relationships as they apply to solutions at constant temperature. Figure 1.12 shows concentration versus time plots for furosemide and Figure 1.13 shows the concentration versus time plots for theophylline. In Figure 1.12 there is no conversion to the most stable crystal form during the experiment. In contrast, in Figure 1.13 the less stable anhydrate converts to the hydrate during the experiment providing unequivocal proof that the hydrate is more stable (less soluble) than the anhydrate. In these examples it is obvious which form of theophylline is the less soluble. Under

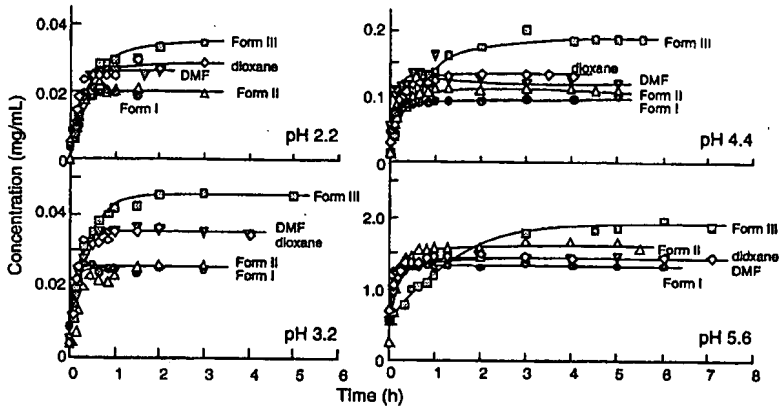


Figure 1.12 Dissolution profiles of the different crystal forms of furosemide in buffer solution at various pH values at 37° C (Matsuda and Tatsumi, 1990).

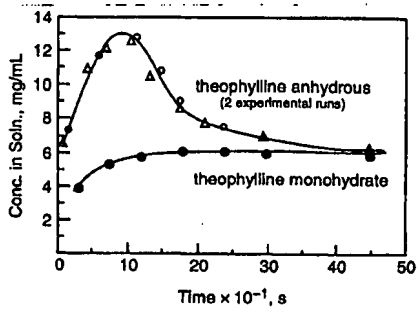


Figure 1.13 Concentration versus time curves for anhydrous and hydrated crystal forms of theophylline in water at 25 °C (Shefter and Higuchi, 1963).

these conditions, this form will never convert to the other, and can therefore also be referred to as the thermodynamically more **stable form.**

When temperature is introduced as a variable, however, further distinctions concerning the relative stability of alternative forms need to be made. The thermodynamic activity (usually observed as solubility) of each form may change quite differently as a function of temperature. **Monotropic** systems are defined as systems where a single form is always more stable regardless of the temperature. **Enantiotropic** systems are defined as systems where the relative stability of the two forms inverts at some transition temperature. These relationships are evident in graphic form (see Figure 1.14).

In actual practice, it is customary to plot log solubility versus $1/T$ for each solid phase (*i.e.*, as a so-called **van't Hoff plot**). These plots give, in most cases, the data in a linear form that lends itself to extrapolation, so that transition points can be determined even when complete data for a given solid phase are unreliable or unavailable. Figure 1.15 shows a van't Hoff plot of solubility versus $1/T$. In this case, there is a transition point where the lines cross and the relative stabilities of the two forms are the same ($\Delta G = 0$). Extrapolation of data 10 K beyond the experimental range is prone to produce large errors and is not reliable.

Transitions from one solid phase to another can occur in the absence of solvent. The mechanisms and kinetics of such solid-state transitions can be very complex and are addressed in Chapters 14, 15 and 20. For example, Kitaigorodskii *et al.* (1965) showed that a pin-prick can initiate the solid-state transformation of α-*p*-dichlorobenzene to β-*p*-dichlorobenzene within a single crystal. The transformation of α- to β-*p*-dichlorobenzene is delineated by the spread of the reaction front from the nucleation site through the crystal. A related process is the thermally-induced rearrangement of the α- to β form of *p*-nitrophenol (Coppens and Schmidt, 1965). In this reaction, needle-shaped single crystals rearrange with the phase boundary moving approximately perpendicular to the needle axis. Grinding or other input of mechanical energy induces the polymorphic transformation of chlorpropamide (Otsuka *et al.*, 1989), fostedil (Takahashi *et al.*, 1985), chloramphenicol palmitate (Kaneniwa and Otsuka, 1985), and several other drugs (Chan and Doelker, 1985).

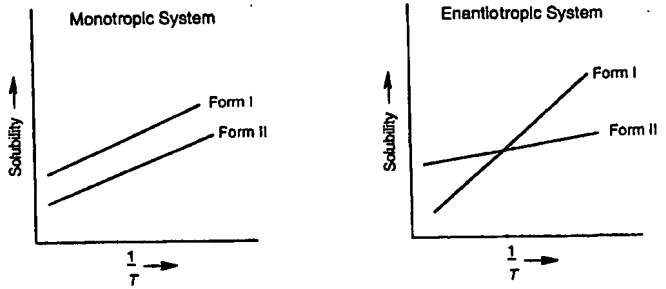


Figure 1.14 Schematic graphs of concentration versus temperature for a monotropic system and an enantiotropic system.

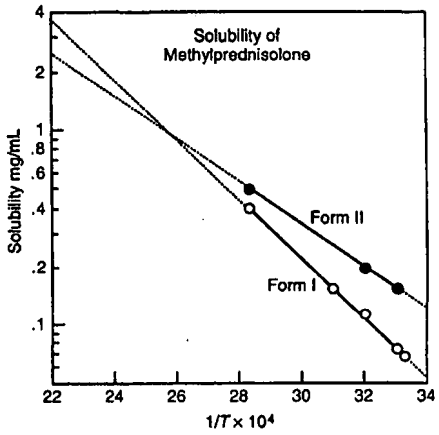


Figure 1.15 A van't Hoff plot of the water solubility of two methylprednisolone crystal forms (log of the solubility as an inverse function of temperature, Higuchi *et al.*, 1963).

D. Other Spontaneous Changes in the Solid State

In addition to the crystal-to-crystal transitions treated above, we should mention another change that can affect properties of drugs: **crystal ripening.** Crystal ripening occurs when the crystal size increases as the solid remains in contact with solution. In this process, larger crystals grow (or ripen) at the expense of smaller crystals. In practice, newly formed crystals contain many "high-energy sites" from the inclusion of impurities, disordered areas (due to rapid growth), and other causes. Crystals less than about one micrometer in size also have excess free energy because of their high surface curvature. These "high-energy" crystals tend to dissolve and then contribute to the ripening process when the material is redeposited on a larger crystal, that is, on a lower free energy site. This process is called "**Ostwald ripening,**" after its discoverer (Ostwald, 1896). The effect of ripening on crystal size is shown in Figure 1.16. Control of this process is important in cases where small particle sizes are needed (*e.g.*, aerosol prod-

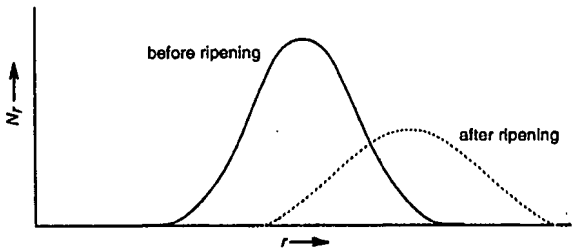


Figure 1.16 Change in crystal size distribution as a result of ripening (Lieser, 1969).

ucts). In addition, ripening can explain particle size changes that take place in suspension during crystallization or wet granulation.

1.6 PROPERTIES OF AMORPHOUS SOLIDS

Amorphous solids have no long-range order, are not crystalline, and therefore do not give a definitive **X-ray diffraction pattern**. The properties of these solids are of interest because they differ considerably from those of their crystalline counterparts. Amorphous solids do not exhibit **birefringence** under crossed polars on the microscope. The most profoundly amorphous solid is a glass in which the atoms and molecules exist in a totally non-uniform array. Amorphous solids have no faces and cannot be identified as either habits or polymorphs. Because the properties of amorphous solids are *direction independent* these solids are called **isotropic**.

Amorphous forms can be prepared by rapid cooling (Fukuoka *et al.*, 1991), grinding (Kitamura *et al.*, 1989; Otsuka and Kaneniwa, 1990), or by lyophilization and spray drying (Haleblian *et al.*, 1971; Pikal, 1990). For example, rapid cooling gives an amorphous form of chloramphenicol palmitate (Kimura and Hashimoto, 1960), as did over 20 other pharmaceuticals (Fukuoka *et al.*, 1991 and references therein). Lyophilization gave amorphous forms of fluprednisolone (Haleblian *et al.*, 1971), antibiotics (Pikal *et al.*, 1977), and proteins (Pikal, 1990).

An amorphous solid is characterized by a unique **glass transition temperature** T_g, the temperature at which it changes from a **glass** to a **rubber**. When T rises above T_g, the rigid solid can flow and the corresponding increase in molecular mobility can result in crystallization or increased chemical reactivity of the solid.

Although amorphous solids often have desirable pharmaceutical properties, such as rapid dissolution rates (Fukuoka *et al.*, 1987), they are not usually marketed because of their lower chemical stability (Pikal *et al.*, 1977) and their tendency to crystallize (Fukuoka *et al.*, 1991), thus overriding any adventitious properties. Nevertheless, in some cases, amorphous forms are used as products. An excellent example is novobiocin (Mullins and Macek, 1960) which exists in a crystalline and an amorphous form. The crystalline form is poorly absorbed and does not provide therapeutic blood levels; in contrast, the amorphous form is readily absorbed and is therapeutically active. Further studies show that the solubility rate of the amorphous form is 70 times greater than the crystalline form in 0.1 *N* HCl at 25 °C when particles <10 μm are used. Table 1.7 (Haleblian, 1975) shows data for the plasma levels of novobiocin's amorphous and crystalline forms and for sodium novobiocin, which also gives detectable plasma levels, but is chemically unstable in solution. Unless special precautions are taken, an amorphous form will sometimes be slowly converted to the crystalline form (Fukuoka *et al.*, 1991 and references therein).

Table 1.7 Dog Plasma Levels of Novobiocin after Administration of Different Novobiocin Forms

	Hours after dose (mg/mL)						
Form	0.5	1.0	2.0	3.0	4.0	5.0	6.0
Sodium novobiocin	0.5	0.5	14.6	22.2	16.9	10.4	6.4
Amorphous novobiocin acid	5.0	40.6	29.3	22.3	23.7	20.2	17.5
Crystalline novobiocin acid	Not detectable at any time						

Haleblian, 1975.

1.7 MOISTURE UPTAKE BY SOLIDS

Some crystalline solids take up water from the atmosphere and are termed **hygroscopic solids** in the literature. Unfortunately, there can be no clear definition of hygroscopic solids because **hygroscopicity** is a relative term. Hygroscopicity is determined by both a kinetic and a thermodynamic term and is a function of the atmospheric relative humidity. In high relative humidities, many solids are hygroscopic. In atmospheres of low humidity, only a few solids will be hygroscopic. Another factor influencing hygroscopicity is surface area and thus porosity. The larger the surface area of the solid, the more rapid the uptake of moisture. This is because solids with larger surface areas have more sites for adsorption of water molecules. Zografi *et al.* (1991) suggested that hydroscopicity not be used and that the relative humidity at which a water-soluble solid **deliquesces** (RH_0) should be used instead. This is a scientific term that can be clearly defined and will not vary from investigator to investigator but is only applicable for highly water soluble solids.

Zografi *et al.* (1991) also described guidelines for the establishment of pharmaceutical compendium water specifications and processes by which water is adsorbed by solids. They suggested that surface water generally does not amount to more than 1 to 3 molecular layers. Since the cross-sectional area of a water molecule is about 0.125 nm^2, 1 to 3 molecular layers would amount to only negligible percentages of water. Table 1.8 shows the calculated layers of water on the surface of a solid as a function of surface area and particle diameter. It is clear from this table that even for the smallest particles, 0.1% water will form a monolayer on the surface. Hence, three layers would only account for about 0.3% water. Obviously, claims for large increases in weight because of surface moisture are not consistent with this observation.

When solids that are not solvates contain large amounts of water, it has been hypothesized that water must be taken up into the solid by disordered or high-energy regions such as defects and amorphous sites. They further suggested that such effects might be exaggerated by manufacturing processes that reduce particle size, such as micronization, milling, or related processes known to increase the number of high energy sites. Of course, some solids can take up so much water during these processes that they become damp or even liquefy at RH_0 (Zografi *et al.*, 1991). This tendency is usually easily detected by microscopic observation. The mass of water necessary for the solid to change from a glass to a more fluid-like system is designated W_g.

The formation of crystal hydrates, of course, is another way for water to be incorporated into a solid. In these cases the water molecules generally occupy a specific crystallographic site in the solid. This site can be determined by X-ray crystallography which thus unequivocally proves the existence and composition of the hydrate. How-

Table 1.8 Calculation of the Number of Molecular Layers of Water on Solid Spheres of Sucrose as a Function of the Surface Area and Particle Diameter.[a]

Number of Layers	Specific Surface Area (m^2/g)	Particle diameter (microns)
1.1	3.8	1
11	0.38	10
42	0.10	38
110	0.038	100

a Density = 1.59 g/cm^3 at 0.1% water content.

ever, many hydrates exist in which the water is located in tunnels within the crystal. The water can be located accurately only by determination of the crystal structure at low temperatures (if even then). In these cases, the water content may change rather easily with changes in relative humidity.

Plots of vapor pressure versus relative humidity are an excellent way to determine the nature of a solid with respect to water sorption (see Figure 1.17). The different kinds of behavior that these plots may be expected to show include:

1. Virtually no water uptake
2. Gradual water uptake, characteristic of an amorphous material or a **nonstoichiometric hydrate** (a hydrate without a simple ratio of water to host molecule)
3. "Stair-step" water uptake, characteristic of a stoichiometric hydrate

Figure 1.18 shows the behavior of two stoichiometric hydrates (a monohydrate and a sesquihydrate) as well as a nonstoichiometric hydrate of sodium cefazolin. In addition, amorphous sodium cefazolin also exists and takes up and loses water in a more or less gradual fashion as described below.

Sorption of water into amorphous solids or regions of a solid involves dispersion or dissolution of the water molecules within a solid. The more polar a solid, the greater the amount of water taken up. Obviously, in such systems the water content depends upon relative humidity. In addition, the amount of water absorbed may not reach equilibrium for several months (Zografi *et al.*, 1991).

In summary, Zografi *et al.* (1991) made the following recommendations with regard to water specifications:

1. A complete profile of relative humidity versus water content (weight) should be reported for all reference standards.
2. For amorphous solids, both T_g and W_g should be reported.
3. For deliquescent solids, the RH_0 and an appropriate warning on the label should be provided.
4. For stoichiometric hydrates, the water specifications should reflect the stoichiometry.
5. Attention should be paid to materials which do not form well-defined hydrates and can take up or lose water as the humidity is varied. Any structural changes that accompany changes in water content should be noted. (Some hydrates can lose water without changing crystal structure. This is due to the formation of an extremely stable crystal packing network by the host molecule.)

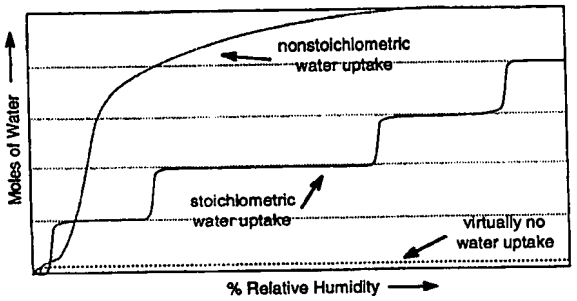


Figure 1.17 Idealized vapor pressure versus relative humidity plot.

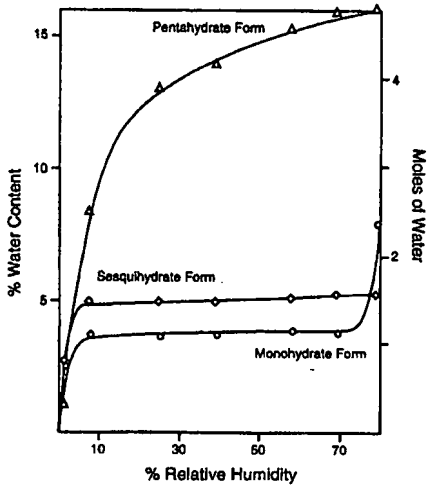


Figure 1.18 Vapor pressure versus relative humidity diagrams for three hydrates of sodium cefazolin. The sesquihydrate and monohydrate behave normally and the "pentahydrate" is actually a nonstoichiometric hydrate (Osawa *et al.*, 1988; Pfeiffer, 1988).

1.8 LYOPHILIZED POWDERS

Many antibiotics, proteins, and other drugs are marketed as lyophilized powders. The process of freezing a solution of the drug and then removing the ice by sublimation yields a product that is low in moisture and high in specific surface area. Although the solid may crystallize during the freeze drying process, the usual product is an amorphous powder. If the solid crystallizes during storage, a slower dissolution rate would be expected.

1.9 PATENTS ON VARIOUS CRYSTAL FORMS

A review of the patent literature indicates that crystal forms and processes involving crystal forms are patentable. Of the approximately 41,000 patents in the *Pharmaceuticals* section of *Chemical Abstracts* (listed prior to August 28, 1991), 122 use the keyword "crystal," 10 use the keyword "polymorph," 27 use the keyword "solvate," and 191 use the keyword "hydrate," or keywords involving higher hydrates. In addition, 79 use the keyword "crystallization." Many of the most interesting patents which were retrieved in this search are listed in Table 1.9. It is important to note that this search is

Table 1.9 Selected Patents on Various Crystal Forms Listed in Chemical Abstracts

Substance	Crystal Form	Utility	Abstract No.
Sodium Acetylsalicylate	crystalline	stable	108:44030*n*
Amoxicillin	anhydrous sodium salt	nonhygroscopic and stable	102:172646*f*
Amoxicillin	pyrrolidone solvate	injectable	96:74631*k*
Amphotericin B	crystals	purification process	112:240473*f*
Azetidine Sulfonic Acid	crystalline anhydrous form	improved stability	99:10852*n*
Azithromycin	dihydrate	nonhygroscopic	111:45265*s*
Beclomethasone	chlorofluorocarbon solvate	stability	94:52972*d*
Beclomethasone	solvates	aerosol formulation	96:91650*h*
Beclomethasone Dipropionate	Freon® solvate	aerosols	113:29296*p*
Beclomethasone Diproprionate	alkane solvates	formulation	102:209431*k*
Beclomethasone Diproprionate	new crystal form	does not form solvates with propellants	94:162747*s*
Benzimidazole Derivative	crystalline	thermostable with small particle size	108:137876*h*
Buspirone·HCl	interconversion	preparation of either form	111:239476*g*
Catechin	monohydrate and anhydrate	formulations	103:59298*b*
Cefadroxyl	anhydrate	preparation	111:239478*j*
Cefadroxyl Monohydrate	monohydrate	preparation	111:239477*h*
Cefahydroxyl Monohydrate	crystalline	preparation from CH_3CN solvate	103:166151*v*
Cefamandole Derivative	γ-form	stability and lack of hygroscopicity	86:78672*r*
Sodium Cefazolin	monohydrate	crystallization process	90:61247*r*
Ceftazidime	anhydrous crystal modification	stability	102:67395*a*
Ceftazidime Intermediate	crystalline $HCl·H_2O$	purification	102:191162*m*
Ceftazidime·$5H_2O$	pentahydrate	increased activity	105:30045*x*
Cefuroxime	crystalline sodium salt	crystallization	102:32299*v*
Cephalexin	crystalline	formulation	84:184895*j*
Cephalexin	monohydrate	stability	74:6404*j*
Cephalexin	*t*-type monohydrate	novel	89:169093*f*

Table 1.9 (continued) Selected Patents on Various Crystal Forms Listed in Chemical Abstracts

Substance	Crystal Form	Utility	Abstract No.
Cephalexin·HCl	monohydrate	immediate release	103:129047*v*
Cephalosporin Antibiotic	heptahydrate sodium salt	improved stability	100:73975*q*
Sodium Cephalothin	crystallization	improved filtration properties	87:141273*z*
A Cephem Carboxylic Acid	hydrates	stability	110:29096*m*
Sodium Cephem-carboxylate	crystals	formulation	103:129069*d*
Cephradine	hydrate	stability	115:35741*n*
Cimetidine	Form A	formulation	100:12669*w*
Cimetidine	Form B	formulation	109:237026*v*
Cimetidine	Form B	preparation	109:176349*d*
Cimetidine	Form Z	formulation	99:10848*r*
Corticosteroids	chlorofluorocarbon solvates	lack of crystal growth in aerosols	85:51743*g*
Cyclosporin	orthorhombic form	sustained release	112:145575*g*
DDI, DDT	monohydrate	high water solubility	115:35706*e*
Deoxycholic Acid	unsolvated crystals	improved formulations	94:162743*n*
Deoxyspergalin	crystalline	improved hygroscopicity, stability, handling	115:15582*h*
Dianemycin glycon	crystalline anhydrous form		106:23267*p*
Dibenzopyrone	polycrystalline form	improved blood levels	86:95990*k*
Famotidine	morphologically homogeneous	homogeneous forms	108:192770*u*
Famotidine	separation of crystal forms	increased activity	111:180678*u*
Flunisolide	crystal form	aerosols	93:138020*h*
Flunisolide	crystal form	aerosols	94:214609*v*
Gabapentin Monohydrate	monohydrate	novel crystal form	113:138572*w*
Gabexate Mesylate	lyophilized crystals	high stability	111:63927*p*
Ibuprofen	crystalline	improved flow properties	102:50901*q*
Inotropic Agent	hydrates	administration	112:204687*v*
Insulin	crystalline suspension	improved release	94:214619*y*

Table 1.9 (continued) Selected Patents on Various Crystal Forms Listed in Chemical Abstracts

Substance	Crystal Form	Utility	Abstract No.
Isoglutamine Derivative	monohydrate	more stable, less hygroscopic	106:12587*8j*
Josamycin	solvent-free crystals	formulation	87:90714*j*
LY163892	dihydrate and trihydrate	preparation and formulation	114:88656*z*
LY163892	solvates	intermediates	114:88639*w*
LY163892 (antibiotic)	monohydrate	formulation	111:20164*6z*
Meclophenoxate·HCl	type I crystals	more stable, less hygroscopic	107:64843*n*
Mefloquine·HCl	polymorph	improved solubility and bioavailability	103:12904*4s*
Methylbutylamine·HCl Derivative	monohydrate	not hygroscopic	107:22331*4j*
Methyldopa Salts	crystalline solvates	crystalline	107:24259*8w*
Mitinone	3 crystal modifications	formulations	110:6377*0m*
Naphthyridine Carboxylic Acid	sesquihydrate	stability	98:59888*x*
Necromodil Na	Form B	stability	108:22683*2h*
4-Oxo-2-azetidinyl Derivative	crystals	crystalline	108:13787*3e*
Penicillin Derivative	hemisolvate	stability	85:13052*3p*
Phenylpropiophenone	spherical crystals	sustained release	115:15598*t*
A piperazine·HCl	new crystal form	increased solubility	105:15880*6p*
Piroxicam	β-form	improved flow properties	111:14047*9y*
Prazosin·HCl	α-form	preparation	99:10849*s*
Pyran-9-one Derivative	polymorphs	particle size	83:15233*4p*
N-Pyridylcarboxyamide	polymorphic monoethanolamine salt	increased stability	105:66460*t*
Quinolone Carboxylate	anhydrate	stability and preparation	112:18577*9h*
Sorbitol	γ-form	improved labeling	95:30396*n*
Steroid	monoclinic or triclinic forms	preparation and formulation	114:21452*1s*
Sulfanetrole Hemihydrate	hemihydrate	no sediment upon storage	107:22331*6m*
(*S*)-Timolol	hemihydrate	preparation	114:49576*d*

by no means comprehensive since several of the most important patents on crystal forms, including those on ranitidine hydrochloride and cefuroxime axetil, did not show up as "hits."

It is clear from Table 1.9 that patents based on solid-state properties have been issued for a wide range of drugs crystallizing in many different crystal forms and having many different uses. The types of drugs included in Table 1.9 range from antibiotics, to antiulcer drugs, to antitumor and antiviral agents, to anti-inflammatory agents. Proteins and various salts are also included. Polymorphs, solvates, hydrates of various types, and lyophilized crystals are among the crystal forms claimed. As might be expected, a wide range of uses is cited. Among the most frequent uses cited are improved formulation, handling, and stability. In addition, there are several patents on crystal forms with reduced hygroscopicity and improved solubility and bioavailability. Patents will no doubt continue to be issued on crystal forms. In fact, it is likely that the number of crystal forms patented will greatly increase since our ability to characterize and understand the crystal forms has greatly improved.

1.10 Solid-State Reactions of Drugs

The scientific discipline of solid-state chemistry of drugs emphasizes studies of the chemical and physical properties of the various solid forms just discussed. These studies include solid-state phase transformations (polymorphic transformations), reactions in which solvent of crystallization is lost or gained, and a broad range of solid-state chemical reactions.

It is necessary to establish criteria for solid-state reactions in order to focus on true solid-state reactions. This will avoid a liquid-state reaction being identified as a solid-state reaction. Morawetz (1966) suggested four criteria for determining whether a reaction is a true solid-state reaction and a fifth and very important criterion can be added from Paul and Curtin (1973):

1. A reaction occurs in the solid when the liquid reaction does not occur or is much slower.
2. A reaction occurs in the solid when pronounced differences are found in the reactivity of closely related compounds.
3. A reaction occurs in the solid when different reaction products are formed in the liquid state.
4. A reaction occurs in the solid if the same reagent in different crystalline modifications has different reactivity or leads to different reaction products.
5. A reaction occurs in the solid phase if it occurs at a temperature below the eutectic point of a mixture of the starting material and products.

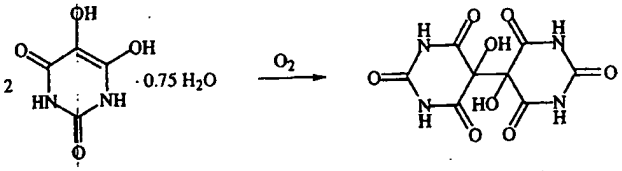
Once it has been established that the reaction is occurring in the solid state, the reaction can be understood in terms of a four-step process (Paul and Curtin, 1973):

1. loosening of the molecules at the reaction site
2. molecular change
3. solid solution formation
4. separation of the product phase

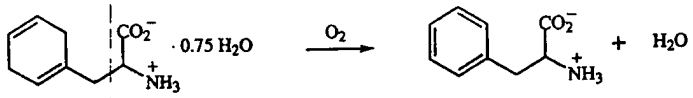
Table 1.10 Solid-State Chemical Reactions of Drugs

Solid-State Oxidations (Chapter 18)

Dialuric Acid (Clay *et al.*, 1982)



Dihydrophenylalanine (Ressler, 1972)



Phorbol Esters (Schmidt and Hecker, 1975)

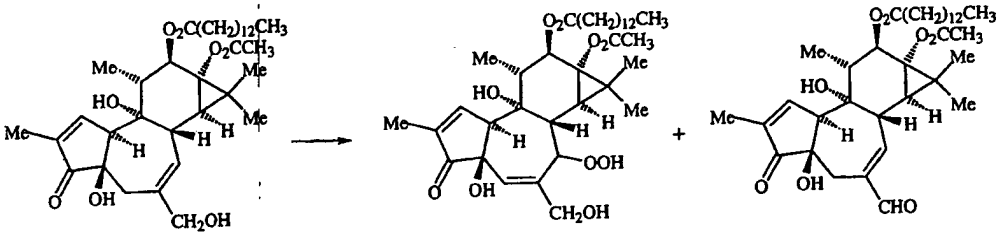
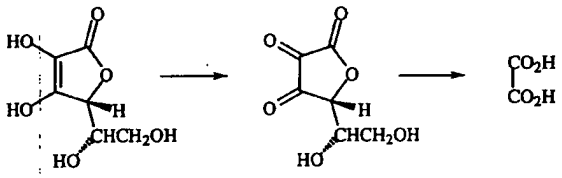
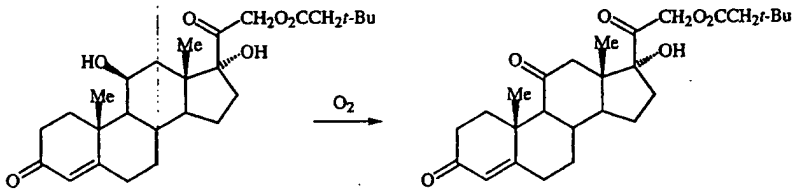


Table 1.10 (continued) Solid-State Chemical Reactions of Drugs

Vitamin C (Rubin *et al.*, 1976)



Hydrocortisone *tert*-Butylacetate (Brenner *et al.*, 1969)



Vitamin D_2 (Kanzawa and Kotaku, 1953)

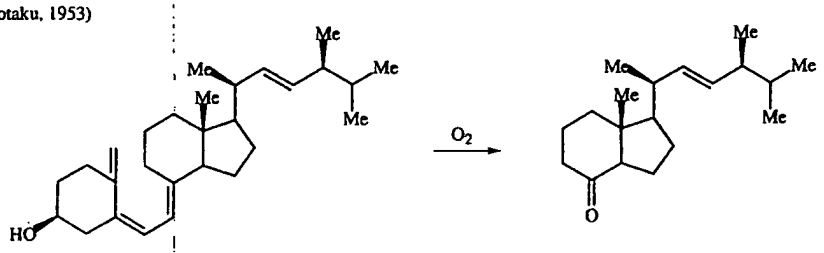
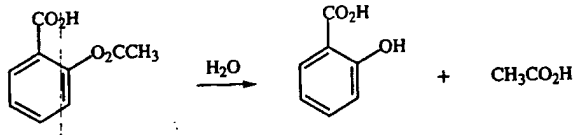


Table 1.10 (continued) Solid-State Chemical Reactions of Drugs

Additions of Gases to Solids—Solid-State Hydrolyses (Chapter 19)

Aspirin (Leeson and Mattocks, 1958)



Nitrazepam (Genton and Kesselring, 1977)

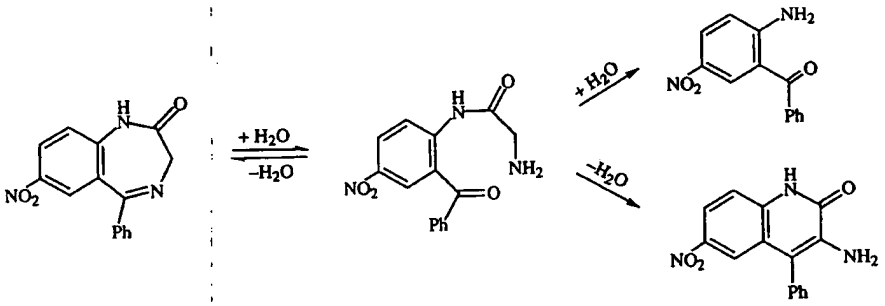
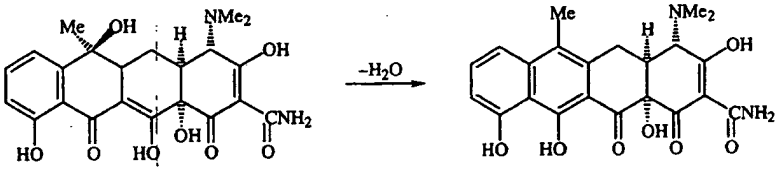


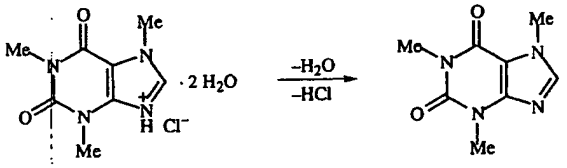
Table 1.10 (continued) Solid-State Chemical Reactions of Drugs

Solid-State Decomposition Reactions: A (solid) → B (solid) + C (gas) (Chapter 20)

Dehydration of Tetracyclines (Simmons *et al.*, 1966)



Dehydrochlorination of Caffeine Hydrochloride (Biedermann, 1883)



Decarboxylation of *p*-Aminosalicylic Acid (Lin *et al.*, 1978)

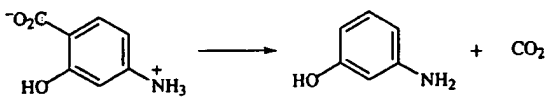
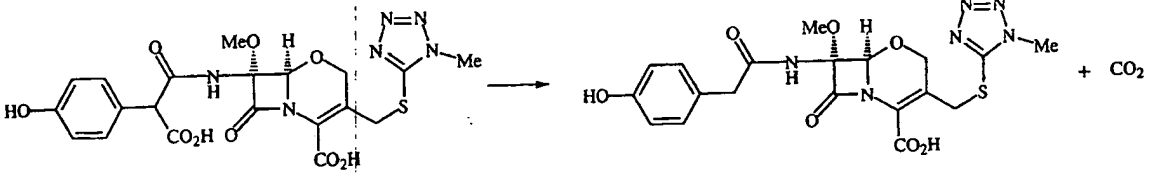


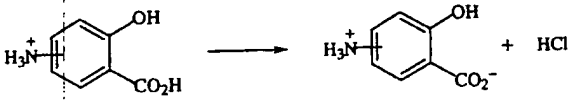
Table 1.10 (continued) Solid-State Chemical Reactions of Drugs

Solid-State Decomposition Reactions: A (solid) → B (solid) + C (gas) (continued)

Decarboxylation of Moxalactam (Pikal and Dellerman, 1989)



Dehydrochlorination of Aminosalicylic Acid Hydrochlorides (Lin *et al.*, 1978)



Solid-State Photochemical Reactions (Chapter 21)

Gibberellins (Adam and Voigt, 1971)

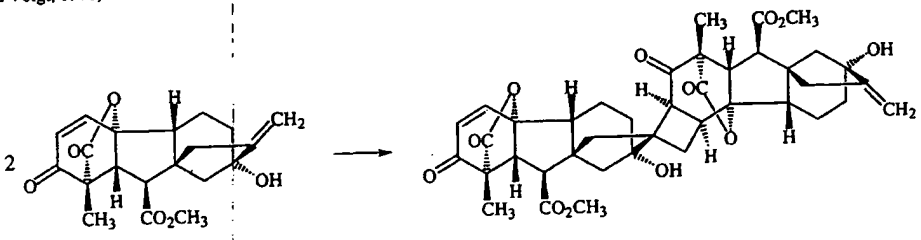
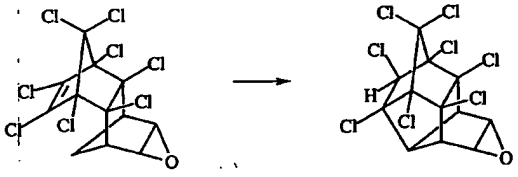


Table 1.10 (continued) Solid-State Chemical Reactions of Drugs

Dieldrin (Benson, 1971)



Nifedipine (Hayase *et al.*, 1994)

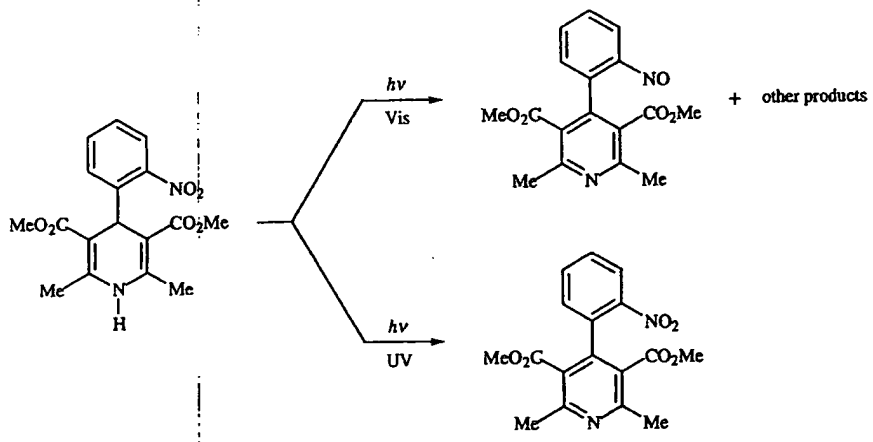
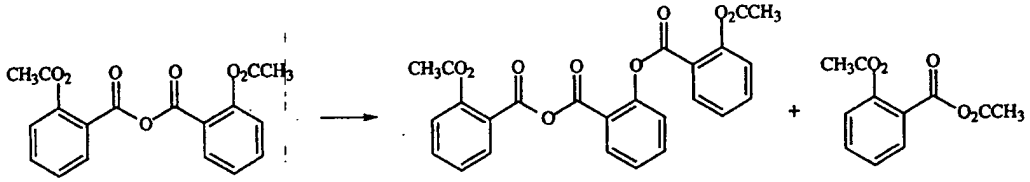


Table 1.10 (continued) Solid-State Chemical Reactions of Drugs

Solid-State Thermal Reactions (Chapter 22)

Rearrangement of Aspirin Anhydride (Garrett *et al.*, 1959)



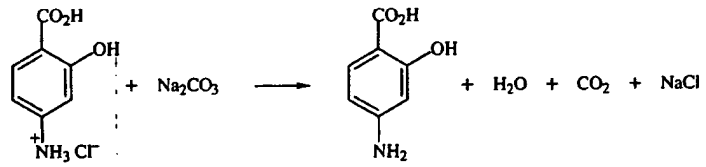
Rearrangement of a Triazenoimidazole (James *et al.*, 1969)

Rearrangement of the Methyl Ester of Tetraglycine (Sluyterman and Veenendaal, 1952)

Table 1.10 (continued) Solid-State Chemical Reactions of Drugs

Solid–Solid Reactions (Chapter 24)

Reaction of *p*-Aminosalicylic Acid Hydrochloride with Sodium Carbonate (Lin *et al.*, 1978)



These four steps are discussed in more detail in Part 5 of this book.

It is important to realize that many solid-state reactions of drugs involve drug degradations which have been studied mostly on the macroscopic level. In fact, few studies aimed at determining the molecular aspects of the solid-state chemistry of drugs have been published. These reactions are of interest because of a desire to prevent such degradation. Even for such common drugs as vitamin D_2 and vitamin A, the structures of only a few of the solid-state degradation products have been published. Therefore, in many respects, the solid-state chemistry of drugs is synonymous with drug degradation.

Table 1.10 summarizes some of the solid-state chemical reactions of drugs and is arranged according to the type of chemical reaction involved. Only solid-state reactions in which the chemical structure of the product(s) is known are included. The classification scheme used in this table is used throughout this book, and each class of reaction is treated in a separate chapter or chapters as noted in the table.

1.11 STABILITY TESTING

One of the practical areas encompassed by the field of solid-state chemistry of drugs is the area of stability testing. Stability tests are conducted on all marketed drugs in order to determine an expiration date after which the drug will not be sold. The FDA has issued guidelines for stability testing (*Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics*, 1987) and the draft of an update (*Guidance for Industry: Stability Testing of Drug Substances and Drug Products*, 1998). These guidelines describe the design and interpretation of stability studies, the content of stability reports, and methods for computing an expiration date.

Manufacturers are required to ensure that the drugs distributed and marketed are of the best possible quality. However, because the phrase "best possible quality" is vague, the government has attempted to define this idea in terms of current good manufacturing practices (cGMP).

Good manufacturing practices were published in the *Federal Register* on September 29, 1978. They require, among other things, that

1. essentially all products must bear an expiration date
2. all products bearing this date must describe the storage conditions under which this date applies
3. the stability-testing program must be defined in writing

An expiration date is required to assure that drug products have the identity, purity, structure, and quality described on the label and package insert during their period of use under the storage conditions described. If the product is subjected to higher temperatures than those described, then the actual expiration date will be sooner than the expiration date on the label.

Generally, stability studies and expiration dates should be determined under conditions approximating normal storage conditions rather than under accelerated conditions. One of the reasons is that elevated temperatures used in accelerated stability tests may be above the eutectic of the reactant or product and may result in misleading

information (see Figure 1.18). Nevertheless, a series of accelerated stability tests can be used to determine the best storage conditions.

For **accelerated stability tests**, each crystalline form and habit of the pure solid as well as solid-solid mixtures of the pure solid with **excipients** and **adjuncts** (additives used to prepare the pharmaceutical product) should be maintained at elevated temperature (different companies use different temperatures) in vials or ampoules. In addition, accelerated studies in which samples are deliberately exposed to light are often carried out. One ampoule or vial should be assayed each day using the most sensitive method available. The experiment should be run for at least two weeks, and the data should be used to determine the rate of decomposition. The rate is conveniently determined using the computer program described in Chapter 23. If the elevated temperature is too close to the melting point of the solid, liquid could form after only a few percent decomposition through the lowering of the melting point by the decomposition products present. Under these circumstances, it is probably best to lower the temperature and extend the study.

The activation energy is also of interest in predicting product stability. For determination of the activation energy, the kinetics (percentage of decomposition versus time) of the solid-state reactions are determined at three or more temperatures. However, the kinetics of solid-state reactions are often much more complicated than in the corresponding solution reactions. Solid-state reactions are usually not clearly zero-order, first-order, etc., but are often of fractional orders. Thus determination of the rate constant at different temperatures is difficult, if not impossible. In addition, because of the slowness of many solid-state reactions, rate studies are usually only carried through one or two half-lives. For this reason, Carstensen (1974) suggests that first-order or zero-order kinetics should be assumed for determination of the activation energy. Thus the rates of decomposition are measured at several temperatures and plotted according to zero-order and first-order kinetics. The equation that gives the best fit by statistical tests is then assumed to give the best rate constants. An attractive alternative approach is to apply the computer program discussed in Chapter 3 to the data.

The rate constants (k) are then plotted versus temperature (T) according to the Arrhenius equation

$$k = Ae^{-E_a/RT} \tag{1.1}$$

where R is the gas constant. From this plot, A (the pre-exponential factor) and E_a (the activation energy) are determined and used to determine the rate constant (k) at the labeled storage conditions. This rate constant is then used to estimate the expiration date.

The reactivity of the compound in solution at elevated temperatures should also be determined to give information about the "intrinsic reactivity" of the drug.

The stability of the drug in light is also usually determined. Each crystalline form and habit of the pure solid and mixtures with adjuncts and excipients is exposed in a suitable light cabinet under the following conditions: inert atmosphere, exposure to air, and exposure to increased humidity humidity. These latter studies can conveniently be performed using a glove bag. Samples are assayed each day using the most sensitive method available.

The container in which the drug has the greatest stability is selected. The best container is determined by measuring the rate of degradation of the drug in various

containers under various storage conditions. Obviously, the container and storage conditions in which the rate of decomposition is slowest should be chosen.

1.12 SUMMARY

This chapter summarizes the scope of the area of solid-state chemistry of drugs. It is clear that this is a broad, relatively unexplored area involving an understanding of crystallization, the properties of crystals, the forces holding crystals together, the properties of other solids (*i.e.*, amorphous solids), the chemical or physical reactions involved, the criteria for solid-state reactions, the kinetics of solid-state reactions, and the broad field of stability testing.

There is a need to develop an understanding of solid-state reactions of drugs in terms of the molecular details of the reactions. Of particular interest is the determination of the molecular parameters that can lead to retardation of the solid-state reactions of drugs and thus render drugs more stable.

It is the aim of the rest of this book to further illustrate the importance and value of molecular understanding of solid-state reactions.

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Claims 1 and 2 also stand rejected under 35 U.S.C. § 103 as obvious over Palmer.

Claims 1 and 2 also stand rejected for both statutory and obviousness-type double patenting, based on the claims of Palmer.

We reverse all of the rejections.

Discussion

The claims are directed to delavirdine mesylate in the S crystal form (claim 1) or in the T crystal form (claim 2). The examiner rejected the claims, under several different rationales, over the Palmer patent.

1. Statutory double patenting

The examiner rejected the claims under 35 U.S.C. § 101 "as claiming the same invention as that of claim 11 of prior U.S. Patent No. 5563142." Examiner's Answer, page 4. The examiner explained that "[i]n the absence of evidence showing otherwise, either of the instant claims may be the same compound recited in US'142." Id.

"35 U.S.C. § 101 prevents two patents from issuing on the same invention.... A good test, and probably the only objective test, for 'same invention,' is whether one of the claims could be literally infringed without literally infringing the other. If it could be, the claims do not define identically the same invention.... If it is determined that the same invention is being claimed twice, 35 U.S.C. § 101 forbids the grant of the second patent." In re Vogel, 422 F.2d 438, 441, 164 USPQ 619, 621-22 (CCPA 1970).

***2** Here, the patent's claim 11 is directed to delavirdine mesylate, without limitation as to crystal form. Instant claims 1 and 2 are directed to delavirdine mesylate in the S and T crystal forms, respectively. Thus, delavirdine mesylate in any crystal form other than S or T, or in a noncrystalline form, would infringe Palmer's claim 11 without infringing either of the claims on appeal. Therefore, the claims on appeal are not directed to the "same invention" as Palmer's claim 11 and are not unpatentable on that basis. The rejection under 35 U.S.C. § 101 is reversed.

2. Anticipation

The examiner rejected the claims under 35 U.S.C. § 102(e) on the basis that "Palmer discloses by name the same chemical compound as the mono methanesulfonate salt. See claim 11 in the US patent. In view of this fact evidence is needed that the prior art compound inherently lacks the characteristics (**x-ray diffraction** spectra recited in claims 1 and 2) relied on herein." Examiner's Answer, page 3.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros., Inc. v. Union Oil Co., 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "An inherent structure, composition or function is not necessarily known.... Insufficient prior understanding of the inherent properties of a known composition does not defeat a finding of anticipation." Atlas Powder Co. v. IRECO Inc., 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999).

"'Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient."' In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981)

(quoting Hansgirg v. Kemmer, 102 F.2d 212, 214, 40 USPQ 665, 667 (CCPA 1939)). When the inherent properties of a prior art product are at issue, "the examiner must provide some evidence or scientific reasoning to establish the reasonableness of the examiner's belief that the functional limitation is an inherent characteristic of the prior art" before the burden is shifted to the applicant to disprove the inherency. Ex parte Skinner, 2 USPQ2d 1788, 1789 (Bd. Pat. App. Int. 1986).

Here, the claims on appeal are not directed to delavirdine mesylate per se, but are limited to the S and T crystal forms of that compound. Therefore, to anticipate the claims, the prior art must disclose delavirdine mesylate in the S and T crystal forms. The examiner has provided no evidence or scientific reasoning to show that the delavirdine mesylate disclosed and claimed by Palmer is in either the S or T crystal form. Therefore, the examiner has not made out a prima facie case of anticipation by inherency.

*3 The examiner's attempt to shift the burden of proof to Appellants was premature. The burden shifts to the applicant only if the examiner can show, by evidence or scientific reasoning, a reasonable basis for concluding that the prior art product meets all the limitations of the claims. The examiner has provided no basis for such a conclusion in this case. The rejection under 35 U.S.C. § 102 is reversed.

3. Obviousness

The examiner rejected the claims under 35 U.S.C. § 103 on the basis that Palmer "discloses the free form of the instant sulfonate salts for use in treating HIV." Examiner's Answer, page 3. The examiner concluded that the corresponding methanesulfonate salt would have been an obvious variant because Palmer "teaches and in fact prefers the use of salt forms for better solubility and crystallinity," and methanesulfonate salts were exemplified for compounds other than delavirdine mesylate. Id., pages 3-4.

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993).

The examiner's obviousness rejection seems to suffer the same infirmity as her anticipation rejection, namely, that it is directed to delavirdine mesylate per se, rather than to the specific S and T crystal forms of delavirdine mesylate that are the subject of the claims on appeal. The examiner has provided no evidence or convincing reasoning why the prior art disclosure of delavirdine mesylate in an undefined state would have suggested the specific S and T crystal forms that are the subject of the instant claims.

Nor has the examiner established that Palmer would have enabled those skilled in the art to make the claimed S and T crystal forms of delavirdine mesylate. Appellants' specification discloses specific conditions for recrystallizing delavirdine mesylate that produce the S and T crystal forms. See pages 2-4 and Examples 1-8. Palmer does not disclose or suggest even the existence of the S and T crystal forms of delavirdine mesylate, let alone how to make them. As stated in In re Hoeksema:

[I]f the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public. In this context, we say that the absence of a known or obvious process for making the

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***1** THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

Board of Patent Appeals and Interferences

Patent and Trademark Office (P.T.O.)
EX PARTE JEFFREY L. HAVENS, DONALD P. SMITH, MICHAEL S. BERGREN AND MARK A. LYSTER
Appeal No. 2001-0091
Application No. 08/732,254

NO DATE REFERENCE AVAILABLE FOR THIS DOCUMENT

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Before WINTERS, ROBINSON, and GRIMES

Administrative Patent Judges

GRIMES

Administrative Patent Judge

ON BRIEF

DECISION ON APPEAL

An oral hearing in this case was scheduled for November 27, 2001. Upon reviewing the case, however, we have determined that an oral hearing will not be necessary and we render the following decision based on the record.

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1 and 2. Claims 1 and 2 are directed to specific crystal forms (form "S" and form "T," respectively) of 1-[5- Methanesulfonamidoindolyl-2-carbonyl]-4-[3-(1-methylethylamino)-2-pyridinyl]-piperazine. monomethanesulfonate salt. [FN1] The claims list the powder **X-ray diffraction** measurements that distinguish the claimed crystal forms from other forms of delavirdine mesylate.

The examiner relies on the following reference:

Palmer et al. (Palmer) 5,563,142 Oct. 8, 1996

Claims 1 and 2 stand rejected under 35 U.S.C. § 102(e) as anticipated by Palmer.

claimed compounds overcomes a presumption that the compounds are obvious, based on close relationships between their structures and those of prior art compounds. *4 399 F.2d 269, 274, 158 USPQ 596, 601 (CCPA 1968) (footnote omitted).

Since the examiner has not established that Palmer would have rendered the claimed invention obvious to those skilled in the art, she has not made out a prima facie case under 35 U.S.C. § 103. The rejection for obviousness is reversed.

4. Obviousness-type double patenting

The examiner rejected the claims for obviousness-type double patenting over Palmer's claim 11. The examiner argues that the instant claims and Palmer's claim 11 are not patentably distinct because they contain "overlapping subject matter" and because Palmer also claims the free form of delavirdine, which is an obvious variant of delavirdine mesylate. Examiner's Answer, page 4.

> Obviousness-type double patenting ... requires rejection of an application claim when the claimed subject matter is not patentably distinct from the subject matter claimed in a commonly owned patent. Its purpose is to prevent an unjustified extension of the term of the right to exclude granted by a patent by allowing a second patent claiming an obvious variant of the same invention to issue to the same owner later.
> In re Berg, 140 F.3d 1428, 1431, 46 USPQ2d 1226, 1229 (Fed. Cir. 1998) (citation omitted, emphasis added).
>
> All proper double patenting rejections, of either type, rest on the fact that a patent has been issued and later issuance of a second patent will continue protection, beyond the date of expiration of the first patent, of the very same invention claimed therein (same invention type double patenting) or of a mere variation of that invention which would have been obvious to those of ordinary skill in the relevant art (obviousness-type double patenting). In the latter case, there must be some clear evidence to establish why the variation would have been obvious.
> In re Kaplan, 789 F.2d 1574, 1579-80, 229 USPQ 678, 683 (Fed. Cir. 1986) (emphasis in original).

Thus, a proper rejection for obviousness-type double patenting requires showing that the later-claimed subject matter "would have been obvious to those of ordinary skill in the relevant art" based on the claims in the earlier patent. As discussed above, the examiner has pointed to nothing in either the claims or the disclosure of the Palmer patent that would have suggested the S and T crystal forms of delavirdine mesylate to a person of ordinary skill in the art. We therefore reverse the rejection for obviousness-type double patenting.

Summary

We reverse all of the rejections because the examiner has not established that the prior art disclosed or suggested the claimed S and T crystal forms of delavirdine mesylate.

REVERSED

BOARD OF PATENT APPEALS AND INTERFERENCES

*5 SHERMAN D. WINTERS

Administrative Patent Judge

DOUGLAS W. ROBINSON

Administrative Patent Judge

ERIC GRIMES

Administrative Patent Judge

FN1. This compound is also known as delavirdine mesylate, Appeal Brief, page 2, and we will refer to it as such.

END OF DOCUMENT